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AMERICAN JOURNAL OF DISEASES OF CHILDREN

AJDC

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Human Immunodeficiency Virus Transmission by Child Sexual Abuse

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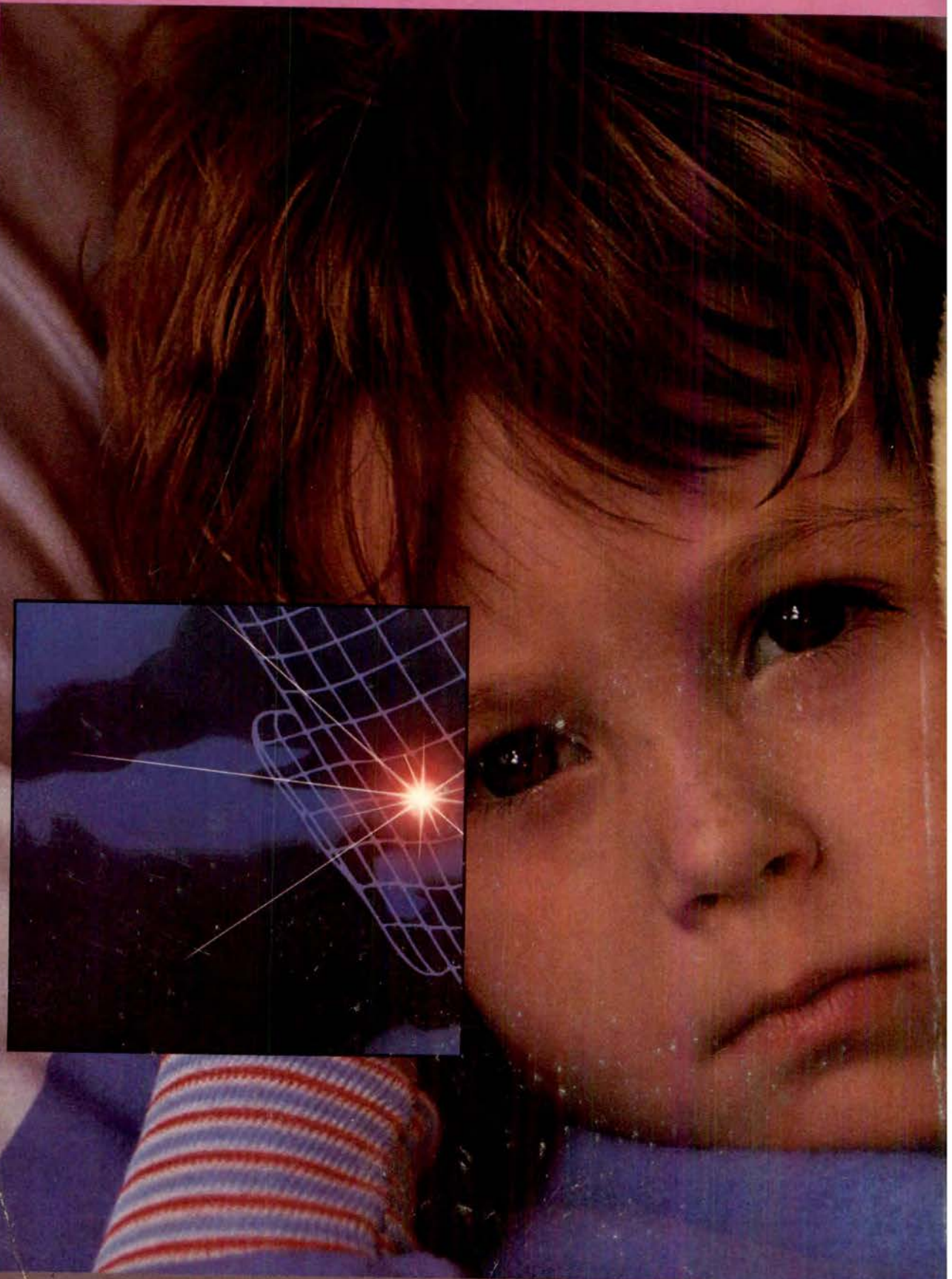
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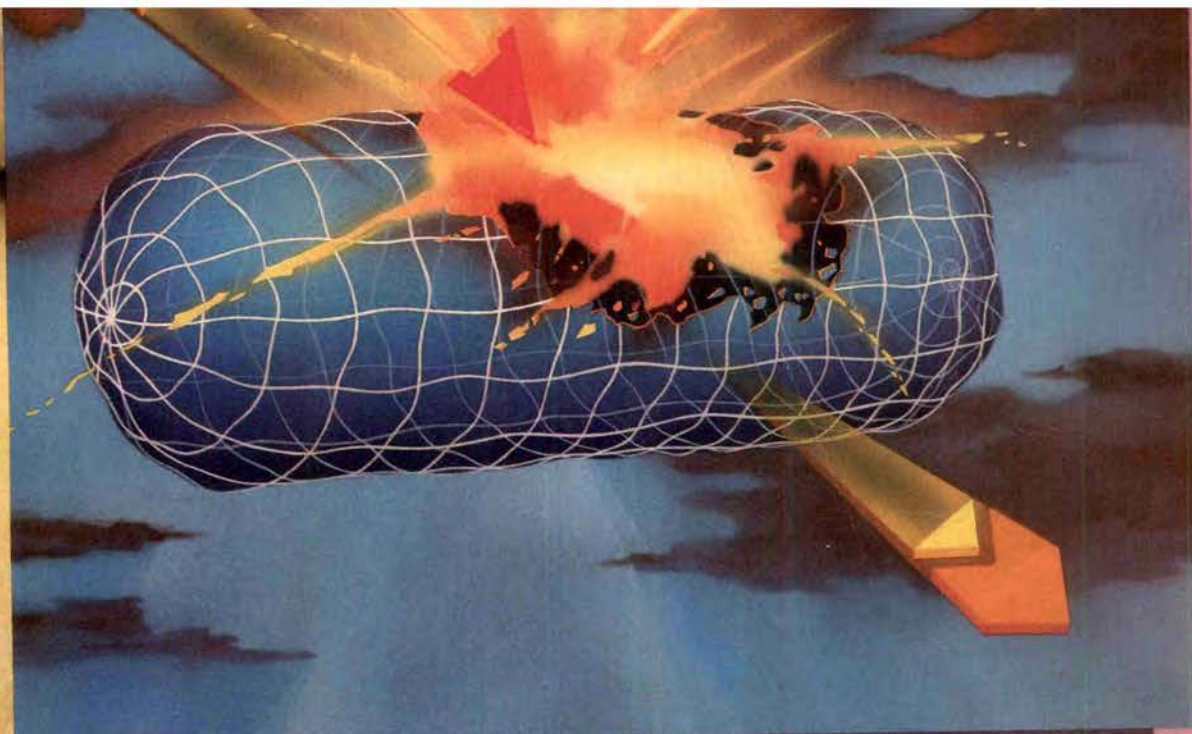
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PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT. INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects.

The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthritis, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one *Augmentin* 250' tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500' tablet every eight hours.

Since both the *Augmentin* 250' and 500' tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250' tablets are not equivalent to one *Augmentin* 500' tablet. Therefore, two *Augmentin* 250' tablets should not be substituted for one *Augmentin* 500' tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* 125' and 250' chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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The AMERICAN JOURNAL OF DISEASES OF CHILDREN (ISSN 0002-922X) is published monthly by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

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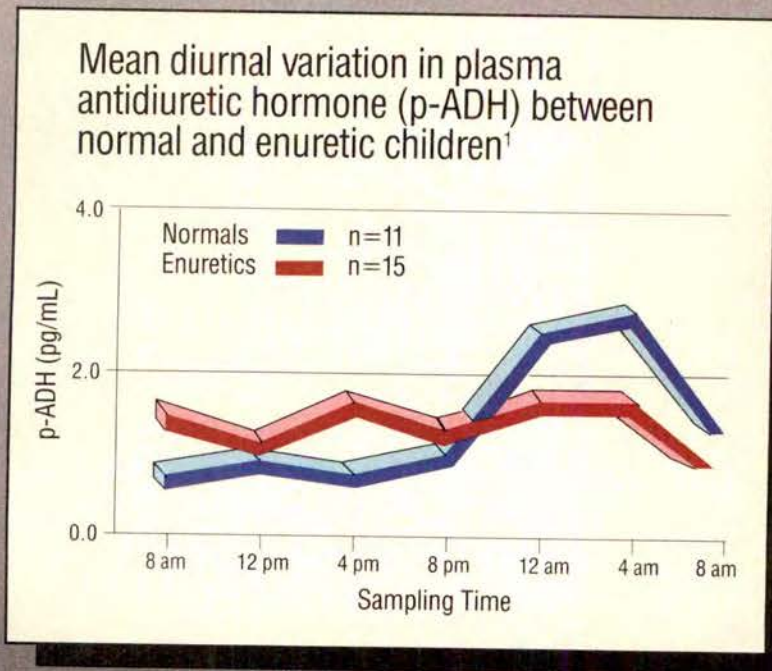
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Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children¹

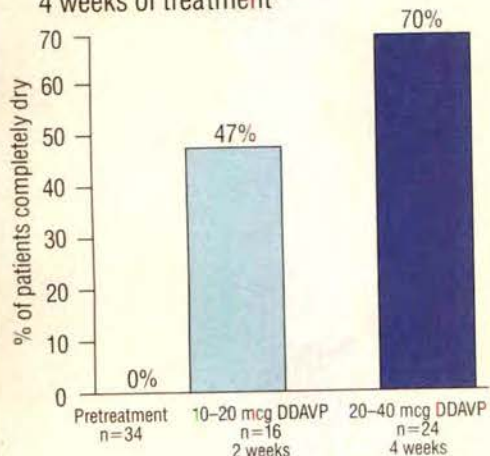


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General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterine action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

	PLACEBO (N=59)	DDAVP 20 mcg (N=60)	DDAVP 40 mcg (N=61)
	%	%	%
ADVERSE REACTION			
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	2
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD₅₀ has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information.

Rev. 6/89

1. Rittig S, Knudsen UB, Nergaard JP, et al: Abnormal diurnal rhythm of plasma vasopressin and urinary output in patients with enuresis. *Am J Physiol* 1989;25(4):F664-F671. 2. Rittig S, Knudsen UB, Sørensen S, et al: Long-term double-blind cross-over study of desmopressin intranasal spray in the management of nocturnal enuresis. In: Meadow SR, ed. *Desmopressin in Nocturnal Enuresis: Proceedings of an International Symposium*. England: Horus Medical Publications; 1988:43-55. 3. Dimson SB: DDAVP and urine osmolality in refractory enuresis. *Arch Dis Child* 1986;61:1104-1107. 4. Data on file, Rhône-Poulenc Rorer Pharmaceuticals Inc. 5. Richardson DW, Robinson AG: Diagnosis and treatment: Drugs five years later: Desmopressin. *Ann Intern Med* 1985;103:228-239.

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EDITORIAL POLICY

The JOURNAL is meant to provide physicians in all specialties who practice pediatric medicine a complete and accurate synthesis of all current research developments and clinical topics pertinent to their practice, as well as an open forum for dialogue on scientific, educational, ethical, and humanistic issues of concern to any intellectual committed to the practice of pediatrics.

All articles published, including editorials, letters, and book reviews, represent the opinions of the authors and do not reflect the official policy of the American Medical Association, the Editorial Board, or the institution with which the author is affiliated, unless this is clearly specified.

*In a small town
outside of Chicago, good news
travels fast. In this
particular case a
family physician was the
messenger. A little girl was
the recipient.*

*Little Nikki was only
9 months old. And her prognosis
for a rich and rewarding
life is excellent.*

EACH YEAR, IT IS ESTIMATED THAT 5,000 CHILDREN DIE FROM RSV COMPLICATED INFECTIONS.¹

Consider treatment with ribavirin aerosol.

For infants hospitalized with lower respiratory tract disease caused by RSV at high risk for **severe or complicated RSV infection**. This includes infants with **congenital heart disease, bronchopulmonary dysplasia** and other **chronic lung conditions**, and certain **premature infants**. In addition, children with **immunodeficiency**, especially those with severe **combined immunodeficiency disease, recent transplant recipients**, and those **undergoing chemotherapy for malignancy**, should also be considered to be at high risk for complicated RSV infection. **Infants hospitalized with RSV** lower respiratory tract disease **who are severely ill**. Since severity of illness is often difficult to judge clinically in infants with RSV infection, determination of the blood gases is often necessary. Infants with **PaO₂ levels of less than 65 mmHg** and those with **increasing PaCO₂ levels** should be considered as candidates for ribavirin therapy. Oximetry may be used as a non-invasive means of determining the arterial oxygen saturation. Infants who might be considered for treatment are those hospitalized with lower respiratory tract disease which is not initially severe, but **who may be at some increased risk of progressing** to a more complicated course **by virtue of young age** (<6 weeks), or in whom prolonged illness might be particularly **detrimental to an underlying condition**, such as those with multiple congenital anomalies, neurologic or metabolic diseases.²

RSVVirazole®
(ribavirin)
aerosol administration

Rapid clinical and viral recovery.

Kathy Foltz, R.N.
Marseilles, Illinois 61341

November 19, 1990

ICN Pharmaceuticals, Inc.
ICN Plaza
3300 Hyland Ave.
Costa Mesa, CA 92626

Dear Sirs:

I am not in the habit of writing letters to drug companies but this time I felt a true need. I want to thank you for how your drug helped my daughter recover from RSV.

I am an O.R. supervisor in a surgery department. When my daughter, Nikki, was 9 months old, she developed what we thought was a cold; wheezing, congestion and fever. One night her wheezing worsened and her breathing became extremely rapid. She got progressively worse and at 4 a.m., I took her to the Emergency room. There, they told me I was doing all the right things and sent us home with antibiotics. At home, Nikki's condition deteriorated--faster respirations and significant retraction. I tried steam, gave the antibiotics and felt absolutely helpless. Years of nursing experience had not taught me what was happening to my daughter. I called our family physician a few hours later and explained Nikki's symptoms. He met us at the Emergency room. Nikki was admitted that night with a diagnosis of pneumonia. Blood cultures were ordered, IV antibiotics given and a test was done for something called RSV.

I had never heard of RSV, but when the test returned positive, our physician immediately ordered a "mist treatment". I have since come to know this mist treatment as Virazole. Nikki was so sick at the initiation of treatment, I was afraid she would give up trying to breathe.

Prayers do get answered. By the next afternoon, her breathing normalized and her color improved--she started smiling and playing again. Nikki remained on Virazole for three days and then we went home.

In a small town, 100 miles south of Chicago, my physician knew about Virazole and was able to treat my daughter close to home. Had he not known, Nikki would have been shipped to a PICU in a large Chicago hospital. The physician, the staff and the drug saved my daughter.

Thank you,

Kathy Foltz R.N.

Kathy Foltz, R.N.

Virazole® (ribavirin) lyophilized for aerosol administration

Rapid response. Rapid recovery.

PRESCRIBING INFORMATION

WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPITATION OF THE DRUG IN THE RESPIRATORY EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

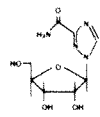
Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is $C_8H_{10}N_4O_5$, and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity *in vitro* against respiratory syncytial virus,¹ influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.² In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the *in vitro* antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.³ The clinical significance of this observation is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies.

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85-98% by 16 µg/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown.

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one metabolite.

Ribavirin administered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 µM, with a mean concentration of 0.76 µM. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 µM, with a mean concentration of 6.8 µM.

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentration.

trations in view of the route of administration.

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concentrations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease.^{3,4} Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.⁴

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement will require shorter hospitalization than would be required for a full course of ribavirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV infection.

The presence of an underlying condition such as prematurity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such patients.

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence^{5,6} or ELISA⁷ before or during the first 24 hours of treatment. Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection.

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribavirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possible emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is unknown.

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only.

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or anti-metabolites has not been evaluated. Interference by

ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of fertility:

Ribavirin induces cell transformation in an *in vitro* mammalian system (Balb/C3T3 cell line). However, *in vivo* carcinogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated.

Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is self-limited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk.

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical studies.

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use:

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator dependence.

Cardiovascular: Cardiac arrest, hypotension, and digitalis toxicity.

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure. Accumulation of fluid in tubing ("rain out") has also been noted.

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD₅₀ in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.³ Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant; oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribavirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml wide-mouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml

with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. **Important:** This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

Virazole® (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15-25°C (59-78°F). Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

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1991 Annual Meeting

The annual meeting of The American Pediatric Society, The Society for Pediatric Research, and The Ambulatory Pediatric Association will be held April 29 through May 2, 1991, at the New Orleans (La) Hilton and Rivergate Convention Center. For further information, contact the APS/SPR Association Headquarters, 2650 Yale Blvd SE, Suite 104, Albuquerque, NM 87106; (505) 764-9099; FAX (505) 842-8227; or the Ambulatory Pediatric Association, 6728 Old McLean Village, McLean, VA 22101; (703) 556-9222.

Impetigo

Sir.—Issues relating to the management of impetigo, a common pediatric problem, continue to be discussed in these pages.^{1,2} Although orally administered antibiotics have been considered optimal therapy for many years, the advent of a novel topical antibiotic, mupirocin, has prompted several clinical trials comparing the efficacy, compliance, cost, and safety of these two treatment modalities. In many of these trials, erythromycin has been used as the prototypic oral agent.³⁻⁶

We recently completed a study of 48 patients with impetigo randomized to receive mupirocin or erythromycin therapy. Twenty-five children received mupirocin and 23, erythromycin. We were interested not only in the comparative efficacy of these drugs, but also in the microbiologic data and antibiotic sensitivities of the bacteria cultured, as recent studies have suggested that *Staphylococcus aureus* is now the most common cause

of impetigo and that a large number of these strains may be resistant to erythromycin.

Patients and Methods.—Both groups in our study comprised mainly urban black children (64% of the mupirocin group and 74% of the erythromycin group). Mean ages were 3.7 years in the mupirocin group (range, 3 months to 10 years) and 4.9 years in the erythromycin group; (range, 5 months to 14 years). Lesions ranged in number from one to 20 (the mupirocin group) and one to 15 (the erythromycin group) per child and were vesicobullous in 32% and 48% of patients in the mupirocin and erythromycin groups, respectively. The mean duration of infection prior to enrollment was 8.5 days in the mupirocin group and 11.6 days in the erythromycin group. The range for both groups was 1 to 30 days. Initial cultures yielded *S aureus* in only 33% of patients, *S aureus* and group A β -hemolytic *Streptococcus* in 41%, group A *Streptococcus* in 12%, and group B *Streptococcus* plus *S aureus* in 4%. In vitro resistance to erythromycin was noted in 10.5% of *S aureus* isolates (five patients). Of these five patients with erythromycin-resistant strains, cultures from four yielded both group A *Streptococcus* and *S aureus*. Three were randomized to the mupirocin group, and a fourth in the erythromycin group who was not followed up could not be evaluated. The fifth patient, with *S aureus* only on culture, was initially in the erythromycin group but was switched to the mupirocin group because of noncompliance in taking oral medication.

Three patients in each of our study groups failed to return for follow-up and therefore could not be evaluated. Of those who were evaluated, 21 (95%) in the mupirocin group and 18 (90%) in the erythromycin group were clinically cured or improved on follow-up. The one patient in the mupirocin group who did not improve had continued spread of lesions and was switched to erythromycin because his culture yielded erythromycin-sensitive *S aureus*. No side effects of medication were encountered in the mupirocin group. Two patients in the erythromycin group were switched to mupirocin, one because of noncompliance and the other because of reported "hysterical attacks" after ingestion of the drug. Two others completed their courses of oral antibiotics, but one complained of stomach pain and nausea and the other, vomiting and irritability. Thus, the incidence of side effects was none in the mu-

pirocin group and 14% (three of 21) in the erythromycin group. Rice et al⁶ also documented a higher incidence of side effects with erythromycin, but, unlike our study, found that noncompliance was greater in the mupirocin group.

Nine patients had draining lesions that were recultured at the first follow-up visit; of those nine cultures, two were positive for the same organisms as in the initial cultures. A second culture of another patient was positive for *S aureus* with a different antibiogram.

Comment.—Of particular interest is evidence of group A streptococcal cause in more than half of our cases (53%). Until the early 1980s, impetigo was considered primarily a streptococcal infection; however, during the past decade, several studies have documented a shift to a predominantly staphylococcal cause. In a study of 243 children from Sydney, Australia, with impetigo, Rogers et al⁷ cultured *S aureus* from 86% of cases (69.6% of cultures yielded *Staphylococcus* only; 15.2% yielded *S aureus* and β -hemolytic streptococci). Less than 50% of these strains were sensitive to erythromycin. Barton and Friedman² identified *S aureus* in cultures from 75% of cases in three consecutive studies of a total of 268 patients, but erythromycin resistance was detected in only 14% of strains. In Barton and Friedman's three series, *S aureus* only was grown from 62%, 46%, and 51% of patients, whereas mixed organisms were grown from 30%, 25%, and 29% of patients. Goldfarb et al⁴ found *S aureus* in 59 (95%) of 62 patients with impetigo. Cultures from nine (14.5%) of these patients yielded mixed organisms. Of the 59 original isolates, 58 (98%) were erythromycin-sensitive in vitro. Eells et al⁸ cultured *S aureus* from 94% of cases in a study reported in 1986.

It is noteworthy that this latter group of investigators identified group A β -hemolytic streptococci (45% in combination with *S aureus*) from cultures of 71% of patients with impetigo in a study 3 years later.⁵ Although 50% of the *S aureus* isolates were erythromycin-resistant, these

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

patients responded well when given erythromycin. This indicates that when cultures yielded both organisms, the *Streptococcus* was the likely causative agent. In view of the resurgence of other streptococcal diseases during the past few years, one might speculate that recent impetigo studies documenting a high percentage of group A streptococci on culture may indicate a reversal in the trend of increasing numbers of cutaneous infections caused by *S aureus*.

As in other studies, we found these drugs to be equally efficacious. However, the issue of drug resistance must be considered when selecting an antibiotic. Fortunately, mupirocin resistance appears to be uncommon.⁹

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Diagnosis of Child Sexual Abuse in Children With Genital Warts

Sir.—We appreciate the review by Boyd¹ on condylomata acuminata in children in the July issue of *AJDC*. This review of the results of the various forms of therapy of genital warts in children was helpful in emphasizing the need for more data regarding the immediate and late results of therapy.

We are writing, in part, to comment on the data regarding the prevalence of sexual abuse in children who develop genital warts. While presenting a case report of any medical condition, the justification for the diagnosis and any critical negative results should be given in sufficient detail to allow the reader to appreciate the basis of the diagnosis. The medical diagnosis of child sexual abuse has been the subject of very active research during the past decade, and the methods for adequate assessment of sexual abuse in a child now include each of the following areas: (1) assessments of medical and behavioral indicators of abuse; (2) a medical examination to identify physical indications of abuse; (3) a microbiologic assessment of other sexually transmissible diseases; and (4) age-appropriate interviews of the child and caretakers by skilled personnel. Some reviews and descriptions of these techniques are given in references 2 through 5.²⁻⁵

Children with genital warts have only infrequently received an assessment employing these techniques, and the methods used in the assessments of children with genital warts have not been described in most previously published reports. The reason for the scarcity of data regarding abuse is that many reports were published prior to the development of adequate diagnostic methods. In one study in which adequate methods were used, 10 (91%) of 11 children with genital warts who presented after the first year of life were proved to have been sexually abused.⁶ The data included proof of abuse in three of the four children who were younger than 3 years at presentation.

We recommend that reports and

reviews of children with genital warts that attempt to identify the status of the child regarding abuse should include only those cases in which the assessment methods which were used are described in detail and which meet current diagnostic standards. Other cases are truly "unknown" and should not appear in the denominator. On this basis, Boyd's conclusion that only 27% of the children had been abused is probably inaccurate. Most of the cases cited were not presented in sufficient detail to allow the reader to determine the adequacy of the evaluation.

The diagnosis and management of child sexual abuse is a rapidly evolving pediatric discipline. Physicians who care for children should be encouraged to establish a relationship with their colleagues in this area so that their patients with genital warts may have the services of a skilled child protection team. Certainly all children with genital warts should be carefully evaluated for sexual abuse.

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In Reply.—I am indebted to Gutman et al for their careful and critical analysis of this work.¹ They may or may not be correct when they propose that the 27% incidence rate of sexual abuse found in this review was too

low. As stated in the article, many authors believe that the presence of condylomata acuminata in children is all but pathognomonic of sexual assault.²⁻⁴ Conflicting evidence has also recently been presented.^{5,6} It should be noted that, while admirable, it was not the point of my article to apply the criteria for child abuse discussed in it to the cases currently in the literature.

The consideration of sexual contact should be entertained when any child presents with venereal warts. As Herman-Giddens² has previously noted, those physicians who deal with pediatric venereal warts are hampered by the fact that methods for ascertaining the means of their acquisition are not foolproof. In fact, one of the references⁷ cited by Gutman et al noted that in almost 21% of their pediatric patients suspected of having been sexually abused, no definite determination could be made, and in an additional 57% it was only "probable." Conversely, the incidence of "benign" venereal wart transmission is also unknown. The pleas of Gutman et al for complete assessment of children with condylomata acuminata and the observation that their presence may portend the existence of other sexually transmitted diseases should be self-evident.

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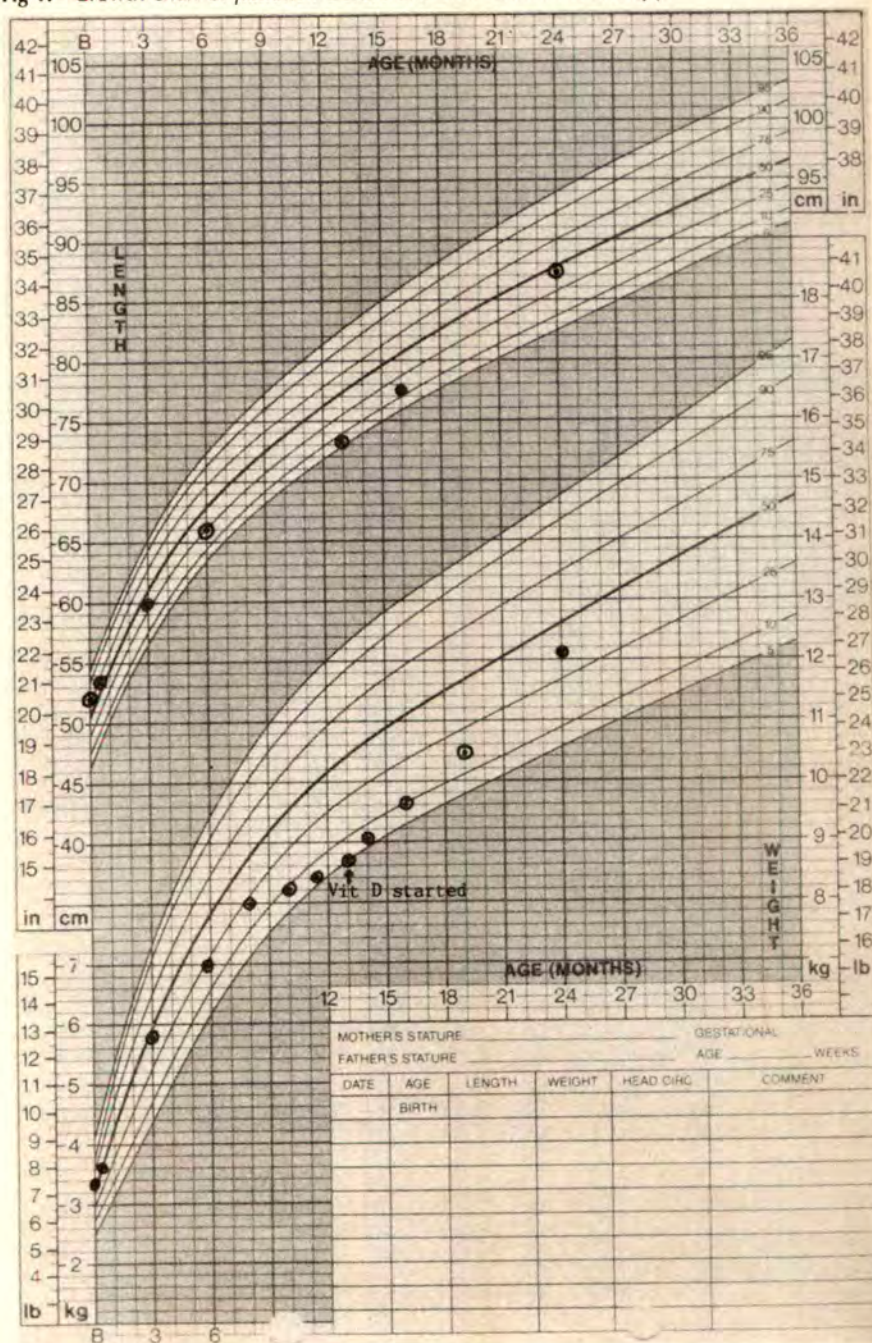
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Rickets Caused by Vitamin D Deficiency in Breast-fed Infants in the Southern United States

Sir.—Rickets caused by vitamin D deficiency in breast-fed infants is rarely reported in patients from the southern part of the United States. Milder

winters, a perennially sunny climate, and liberal vitamin D supplementation are the most likely reasons for this low incidence. We report four cases of rickets in breast-fed black infants who received no vitamin D supplementation. Except for one patient, there was no history of patients being overdressed or deprived of sunlight exposure. Lack of familiarity with the disease, stemming from the rarity of its occurrence in warm climates,

Fig 1.—Growth chart of patient 1 before and after vitamin D therapy.



Pertinent Clinical and Biochemical Data*								
Case No.	Age at Diagnosis, mo	Duration of Breast-Feeding, mo	Ca, mmol/L (2.25-2.7)	P, mmol/L (1.45-2.1)	ALP (<300 IU/L)	25OHD, nmol/L (37-137)	PTH, C-Terminal (<340 ng/L)	Clinical/Radiologic Findings
1	13	12	2.25	1.1	1868	12	456	FTT at 9 months; inability to walk, muscle weakness at 12 months; rickets diagnosed at 13 months; roentgenogram consistent with rickets
2	16	13	2.27	1.0	952	10	434	Diagnosed with motor neuron disease at 13 months; walked at 14 months; significant bowing of leg, enlargement of knee and wrist at diagnosis of rickets, 16 mo; roentgenogram consistent with rickets
3	8	6	2.50	1.5	2797	NA	450	FTT at 8 months; roentgenogram consistent with rickets
4	12	8	2.50	1.4	392	22	NA	FTT, bowing of leg at 1-y physical examination; walked at 10 months; roentgenogram consistent with healing rickets

*No vitamin D supplements were taken by the patients. Normal ranges and values are shown in parentheses. Ca indicates calcium; P, phosphate; ALP, alkaline phosphatase; 25OHD, 25-hydroxycholecalciferol; PTH, parathormone; FTT, failure to thrive; and NA, not available.

probably delayed the diagnosis in two cases.

Patient Reports.—PATIENT 1.—A 13-month-old black boy presented to the Pediatric Clinic of the United States Air Force (USAF) Medical Center, Keesler Air Force Base, Miss, with failure to thrive, inability to walk, and muscle weakness. He had been delivered after a full-term pregnancy. He had visited the clinic many times for the treatment of upper respiratory and ear infections. At 9 months, he fell from the growth chart for both height and weight and continued to fall from the weight curve at a subsequent visit (Fig 1). At age 13 months, parental concern was heightened by the patient's failure to thrive and inability to walk.

The infant was breast-fed for 1 year, and his diet was intermittently supplemented with formula. No vitamin supplement was prescribed; solid food was introduced at age 6 months, but the infant was described as a "very picky eater." There was no history of undue restriction from sunlight. Pertinent physical findings included hypotonia, proximal muscular weakness, minimal bowing of the legs, an open anterior fontanelle, and rachitic rosary. He was at the 5th percentile for his age for height and weight. Roentgenographic examination of the leg and wrist revealed classic rachitic changes; biochemical data are provided in the Table. Vitamin D, administered in a dosage of 4000 IU/d, was prescribed initially and gradually reduced to a maintenance dosage of 400 IU/d after 3 months. Alkaline phosphatase (ALP) returned to normal levels within 3 months, and significant

healing of the rickets (as demonstrated on roentgenography) and satisfactory weight gain were noted after 1 month of therapy (Fig 1).

PATIENT 2.—A 16-month-old black girl was referred to the Pediatric Endocrine Clinic of the USAF Medical Center because of significant bowing of the legs, weakness, "funny gait," enlargement of the wrists and knees, and poor weight gain.

The child had been delivered after a full-term pregnancy and was breast-fed for 13 months; solid food was introduced at age 6 months. Because of hypotonia and inability to walk at age 13 months, she was taken to a neurologist, who considered the diagnosis of muscle disease/motor neuron disease. However, the patient started walking at age 14 months. At age 16 months, the parents noted significant bowing of the legs, which prompted the visit.

Results of a physical examination revealed a child at the 5th percentile for her age for both weight and height. Pertinent positive findings were significant bowing of the legs, enlargement of both the wrists and knees, rachitic rosary, waddling gait, and low muscle mass with mild weakness and hypotonia. Biochemical and roentgenographic findings were consistent with rickets caused by vitamin D deficiency (Fig 2 and Table). The child was administered 4000 U of vitamin D daily. Levels of ALP returned to normal by 8 weeks after initiation of therapy with satisfactory healing of the bone (as demonstrated on roentgenography) by that time. Increases in height and weight were



Fig 2.—A roentgenogram of patient 2 shows symmetrical marked metaphyseal flaring and irregularities involving both lower extremities in association with a metaphyseal band of lucency. There is also significant deformity of the lower tibia.

noted in follow-up visits. Vitamin D intake was gradually reduced to 400 IU/d by 10 weeks after initiation of therapy.

PATIENT 3.—An 8-month-old black girl was brought to her pediatrician because of poor weight gain (her height and weight

were below the 5th percentile for her age). She had been delivered after an uncomplicated 37-week gestation and was breast-fed until age 6 months without vitamin D supplementation; solid food was introduced at 5 months, but her intake was poor. Results of physical examination were unremarkable. Laboratory and roentgenographic findings were consistent with rickets. The patient was administered a multivitamin drop (400 U of vitamin D) with iron daily. At age 10½ months, the infant returned to the clinic. Weight gain was not satisfactory and her ALP level remained elevated (1339 IU/L). The vitamin D dosage was increased to 1000 U/d. On a follow-up visit at age 12 months, a 1.5-kg weight gain and a significant increase in height were noted. Her ALP level had fallen to 486 IU/L and there was near complete healing of the rickets (as demonstrated on roentgenography).

PATIENT 4.—A 12-month-old black boy was taken to the Pediatric Clinic of the USAF Medical Center for a routine physical examination. He was a twin delivered after 38 weeks' gestation. His dietary history was remarkable for breast-feeding through the first 8 months of life without vitamin D supplementation. Solid foods were introduced at age 4 months. His mother reported restricted sun exposure during his first 8 months of life; the patient walked at age 10 months.

Results of physical examination were remarkable for bilateral bowing of the legs; height and weight were at the 5th percentile for the patient's age. Results of the remainder of the examination were within normal limits. Roentgenographic and biochemical findings were consistent with resolving rickets.

The child was administered 400 IU of vitamin D per day. At follow-up 3 weeks later, a 0.9-kg weight gain was noted and his ALP level had fallen from 392 to 251 IU/L.

Comment.—Breast-feeding has increased during the past decade in the United States.¹ Nevertheless, controversy exists concerning the development of rickets in the breast-fed infant. There are articles recommending^{2,3} and disputing^{4,5} routine vitamin D supplementation in the breast-fed infant. Human milk contains adequate quantities of calcium and phosphorus for bone mineralization and skeletal growth of full-term infants.² However, the vitamin D content of breast milk is generally low.^{2,5} Despite this, breast-fed infants usually do not develop nutrition-related rickets. The American Academy of Pediatrics⁶ recommends that breast-fed infants receive vitamin D supplements if they do not receive adequate sunlight exposure or if the maternal diet is low in vitamin D.

However, sporadic cases of nutrition-related rickets continue to appear in the American literature. Most of the reports are from the North and Northeast, and the majority of the patients are black.⁷ There are only rare reports of rickets in the South.

Several studies^{8,9} have emphasized the importance of environmental and other risk factors in the development of nutrition-related rickets. These include darkly pigmented skin, dwelling in the inner city, excessive clothing, restricted sunlight exposure, and maternal vegetarian or other unusual diet. Identifiable risk factors for all of our patients included dark skin, prolonged breast-feeding without vitamin D supplementation, and poor intake of solid foods.

Three of our patients had adequate sunlight exposure, but each still developed rickets. This emphasizes the fact that breast-fed black infants without vitamin D supplementation require much more exposure to sunlight to prevent rickets than originally estimated by Specker et al.¹⁰ They estimated that an infant wearing a diaper needs only 30 minutes of sunshine per week to maintain normal levels of 25-hydroxycholecalciferol, while a fully clothed infant without a hat needs 2 hours of sunlight exposure per week. However, black infants in their study had significantly lower serum 25-hydroxycholecalciferol levels than their white counterparts. This finding may be explained by high melanin concentrations in dark-skinned people.¹¹ High melanin concentrations may limit vitamin D synthesis by competing with 7-dehydrocholesterol for UV photons.^{11,12} Clemens et al¹² have demonstrated that blacks may need six times more exposure to UV light than whites to maintain similar levels of vitamin D.

Adequate vitamin D in the diet and/or vitamin D supplementation to the lactating mother are also important factors in the prevention of rickets in the breast-fed infant.¹¹ The vitamin D levels of the mothers of our patients were not known, although two gave histories of taking multivitamins during breast-feeding. The amount of vitamin D necessary for a lactating mother to prevent rickets in her breast-fed infant may vary with different geographic locations.¹³ However, the Food and Nutrition Board of the National Academy of

Science recommends 600 IU of vitamin D daily in an adolescent who is pregnant or lactating.¹⁴

Another effective strategy in the prevention of nutrition-related rickets is direct supplementation of the infant's diet. Reasons for not providing supplementary vitamin D were not clear in two of our patients. In the other patients, however, pediatricians did not believe vitamin D supplementation necessary because the patients lived in warm climates. This trend is not uncommon among young physicians. In one survey taken in San Diego, Calif, 29% of pediatricians did not routinely prescribe vitamin D supplements to breast-fed infants, and those in practice for fewer than 10 years were even less likely to do so.⁹ The fact that diagnosis was delayed in two of these infants even though they were receiving regular pediatric supervision illustrates the lack of awareness in the medical profession about this condition. Two of these described infants presented with classic features of rickets (ie, growth failure, hypotonia, muscle weakness, and delayed motor development¹⁵), yet this diagnosis was not considered until the skeletal manifestations of rickets were evident. In the third patient, rickets was correctly diagnosed, but treatment was inadequate. The fourth patient was diagnosed to have rickets, but only after healing had already begun. Rickets is a systemic disease¹⁶; the standard pediatric textbooks, however, emphasize mainly the skeletal manifestations of rickets. Many times, however, skeletal manifestations lag behind other signs. Failure to recognize these signs will lead to misdiagnosis and late diagnosis of rickets, as these patient reports illustrate.

Although rickets caused by vitamin D deficiency is rare, it still exists, and subclinical rickets may be more frequent than is generally recognized. Patients may not present with the classic signs and symptoms of rickets; therefore, physicians caring for infants and children must be familiar with the early manifestations of rickets to provide an early diagnosis of the condition. Because the disease is preventable, prevention should be the goal. Although it may be true that some breast-fed infants do not routinely need vitamin D supplements, we do recommend 400 IU of supplementary vitamin D per day

in all breast-fed black infants regardless of geographic location. This dose of vitamin D is safe,^{7,17} cost-effective,⁷ and proven adequate to prevent rickets caused by vitamin D deficiency in breast-fed infants.

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We wish to thank Sandra Amidon for her typing expertise, which made the manuscript possible.

The views expressed in this article are those of the authors and do not reflect the official policy or position of the Air Force, the Department of Defense, or the US government.

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In Bronchitis and Otitis Media*

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- **Highly active against key respiratory pathogens^{†7-9}**
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* Due to susceptible organisms.

† Although a useful guide, *in vitro* activity may not correlate with clinical response.

SUPRAX may be administered as a single dose, once a day, or in divided doses bid if preferred.

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SUPRAX® cefixime/Lederle

BRIEF SUMMARY. Please see package insert for full Prescribing Information
INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella* (Branhamella) *catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S. pneumoniae* and *H. influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S. pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S. pneumoniae* was isolated from 47% of the patients, *H. influenzae* from 34%, *B. catarrhalis* from 15%, and *S. pyogenes* from 4%.

The overall response rate of *S. pneumoniae* to cefixime was approximately 10% lower and that of *H. influenzae* or *B. catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H. influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome			
Organism	Cefixime ^(a) 4 mg/kg bid	Cefixime ^(a) 8 mg/kg qd	Control ^(a) drugs
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1 ^(b)
<i>Moraxella</i> (Branhamella) <i>catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>Streptococcus pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *H. influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuation, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinistix[®], Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix[®] or Tes-Tape[®]).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Oral Liquid **PEDIAPRED®** (prednisolone sodium phosphate, USP)

Brief Summary

DESCRIPTION: PEDIAPRED Oral Liquid is a dye free, colorless to light straw colored, raspberry flavored solution. Each 5 ml (teaspoonful) of PEDIAPRED contains 6.70 mg prednisolone sodium phosphate (5.00 mg prednisolone base) in a palatable, aqueous vehicle.

INDICATIONS AND USAGE: PEDIAPRED Oral Liquid is indicated in the following conditions:

- Endocrine Disorders:** Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; hypercalcemia associated with cancer; nonsuppurative thyroiditis.
- Rheumatic Disorders:** As adjunctive therapy for short term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; post-traumatic osteoarthritis; synovitis of osteoarthritis; epicondylitis.
- Collagen Diseases:** During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; systemic dermatomyositis (polymyositis); acute rheumatic carditis.
- Dermatologic Diseases:** Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis; severe seborrheic dermatitis.
- Allergic States:** Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; drug hypersensitivity reactions.
- Ophthalmic Diseases:** Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis; keratitis; allergic corneal marginal ulcers; herpes zoster ophthalmicus; iritis and iridocyclitis; choroiditis; anterior segment inflammation; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia.
- Respiratory Diseases:** Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; aspiration pneumonia.
- Hematologic Disorders:** Idiopathic thrombocytopenic purpura in adults; secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia; Erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia.
- Neoplastic Diseases:** For palliative management of: leukemias and lymphomas in adults; acute leukemia of childhood.
- Edematous States:** To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus.
- Gastrointestinal Diseases:** To tide the patient over a critical period of the disease in: ulcerative colitis; regional enteritis.
- Nervous System:** Acute exacerbations of multiple sclerosis.
- Miscellaneous:** Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement.

CONTRAINDICATIONS: Systemic fungal infections.

WARNINGS: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and a lack of antibody response.

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

PRECAUTIONS: General: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinitiated. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for Patients: Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision, to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection.

Drug Interactions: Drugs such as barbiturates which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of PEDIAPRED be increased.

Pregnancy: Pregnancy Category C - Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats and rabbits have yielded an increased incidence of cleft palate in the offspring.

Nursing Mothers: Prednisolone is excreted in breast milk, but only to a small (less than 1% of the administered dose) and probably clinically insignificant extent. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

ADVERSE REACTIONS:

Fluid and Electrolyte Disturbances

Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension

Musculoskeletal

Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis

Dermatologic

Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests

Metabolic

Negative nitrogen balance due to protein catabolism

Neurological

Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache

Endocrine

Menstrual irregularities; development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes

Ophthalmic

Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos

OVERDOSEAGE: The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children. Treatment of acute overdose is by immediate gastric lavage or emesis. For chronic overdose in the face of severe disease requiring continuous steroid therapy the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

CAUTION: Federal law prohibits dispensing without prescription.

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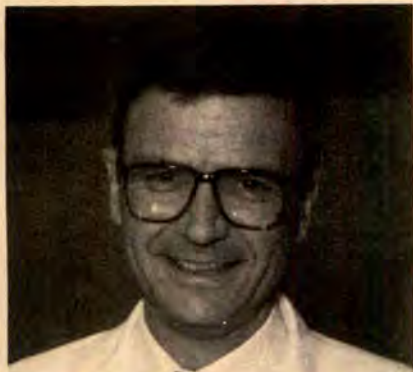
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Tell the Whole Story



John D. Johnson

John Johnson has been a faithful member of our editorial board for 6 years. He has been a stalwart in refereeing manuscripts in neonatology, an area in which we receive more articles than any other. In every instance, his opinion has been insightful, appropriately critical, and often of great help to authors. It is fitting that his essay in this issue deals with observations that he has made in this process.

John is currently professor and chairperson of the Department of Pediatrics at the University of New Mexico in Albuquerque, and pediatrician-in-chief at Children's Hospital of New Mexico. He has received many teaching, clinical, and research awards. He has also been active in regional, national, and international organizations. Most recently, he was elected chief of staff at the University of New Mexico Medical Center (1989-1991), and was named an ex-officio member of the Board of Trustees of the University of New Mexico Hospital (1989-1990). He is a current recipient of a research grant from the National Institutes of Health, Bethesda, Md, to the Rocky Mountain Center for the Biology of Development (1990-1995). He recently reported on fetal hyperinsulinemia and protein turnover in a rat model and on increasing breast milk for premature infants using a unique relaxation imagery audio tape.

As my term on the editorial board of *AJDC* draws to a close, a series of observations and experiences prompts me to make some recommendations to authors and to university administrators, tenure and promotions committees, department chairpersons, and National Institutes of Health (NIH) administrators. During the past several years, I have served on promotions committees and as a department chairperson, and have reviewed numerous manuscripts submitted to *AJDC* as a member of the editorial board. This combination of experiences has convinced me that changes are needed in the academic milieu that would benefit faculty members aspiring to promotions and tenure, and provide promotions committees and deans with more objective and valid indexes when considering the research productivity of faculty members as one of the three legs of our academic tripartite stool. My observations are as follows:

1. Authors often present an incomplete "story" when submitting manuscripts. Results of a single study are "presented" to the medical literature as a series of related overlapping studies. A single piece of research is broken down into a series of reports, each of which, to quote Broad,¹ is the "least publishable unit." The coherent whole is frequently missed unless readers are diligent in tracking the authors' publications. This fragmentation of information detracts from the overall message the authors have to provide, and has significant economic implications for publishers, libraries, and indexes.

2. Such fragmentation is, in fact, encouraged by the "weight" that tenure and promotions committees give to the quantity rather than the quality of publications. With some exceptions, it is easier for these committees to weigh or count the number of publications than to critically identify and assess the importance of the candidates' best research efforts. The same is true for study sections of the NIH and other granting agencies.

3. Deans and department chair-

persons have not, for the most part, insisted on change in this archaic system. Their passive acceptance of this process only accentuates the anxieties of faculty aspiring to promotions and tenure and, in turn, promotes the fragmentation existing within the biomedical literature that I deplore.

My recommendations follow logically:

1. Authors should be encouraged to "tell the whole story" in each of their publications. The critical readers will appreciate and acknowledge the wisdom of this approach.

2. Promotions and tenure committees should set very specific criteria for evaluation of research productivity, eg, considering only those three to five publications that the nominee and his or her chairperson consider most significant. Weight and quantity should be disregarded. Thereby, members of these committees could concentrate their own efforts on a critical evaluation of this small number of publications. This same recommendation extends to study sections of the NIH, National Science Foundation, and other agencies.

3. Chairpersons and deans must buy into this process and agree to instruct the promotions and tenure committees that more is not necessarily better. Instructions to the committees and to chairpersons by deans must stress quality rather than quantity.

These suggestions are not novel. Some, but very few, academic institutions have already adopted such policies. Angell² has made similar suggestions in the internal medicine literature. I only wish to make a similar plea to academic pediatrics—authors should be allowed and encouraged to tell the whole story and the policies of universities and granting agencies should, in fact, require them to do so.

References

1. Broad WJ. The publishing game: getting more for less. *Science*. 1981;211:1137-1139.
2. Angell M. Publish or perish: a proposal. *Ann Intern Med*. 1986;104:261-262.

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Human Immunodeficiency Virus Transmission by Child Sexual Abuse

Laura T. Gutman, MD; Karen K. St Claire, MD; Chris Weedy, MSW; Marcia E. Herman-Giddens, PA, MPH; Barbara A. Lane, MSN; Jeanne G. Niemeyer, MSW; Ross E. McKinney, Jr, MD

● During 1987-1989, 14 (14.6%) of the 96 children who tested positive for the human immunodeficiency virus (HIV) and were followed up by the Duke University (Durham, NC) pediatric acquired immunodeficiency syndrome team were confirmed to have been sexually abused. Every sexually abused child was evaluated for each of five modes of HIV transmission, and in nine children the pathway was identified. Four of the study children acquired HIV from child sexual abuse and in six, abuse was a possible source. Transmission by child sexual abuse was the most frequent of the proven modes of acquisition of HIV in this population. The other proven modes of acquisition were vertical transmission ($n=3$) and HIV-contaminated blood transfusion ($n=2$). Twelve males were identified ($n=8$) or suspected ($n=4$) of being perpetrators. Three knew themselves to have HIV at the time of an assault and eight were aware that the child had HIV at the time of an assault. There was no indication from any child that "safe sex" precautions had been observed. Children with HIV infection had multiple risk factors for abuse or neglect. The sociological descriptors of the lives of the 14 abused children showed multiple known risk factors for sexual abuse that also overlapped with known risk factors for or sequelae of the acquisition of HIV infection. These included drug abuse and alcoholism in the home, prostitution of a parent, lack of parenting, poverty, and chronic illness of the child. Prevention efforts should recognize that children as well as adults are at risk for sexually transmitted HIV infection.

(AJDC. 1991;145:137-141)

The Duke University (Durham, NC) pediatric acquired immunodeficiency syndrome (AIDS) team began accepting pediatric patients in 1987 and by December 1989 had a census of 96 patients who showed positive results to the human immunodeficiency virus (HIV) antibody test and were known to the AIDS team social worker. These children were at all stages of HIV-related illness and ranged in age from newborn to 17 years. All children received integrated multidisciplinary services that delivered

optimal therapy and treatment of the complex problems that characterize children with AIDS.

During this period, 14 children from the AIDS population were confirmed to have been sexually abused. The medical and social conditions of the lives of the abused children were reviewed for known risk factors for the acquisition of HIV and for child sexual abuse (CSA). This study describes the results of the evaluation of the sexually abused children, the circumstances surrounding the abusive experiences, the perpetrators, and the data regarding the means by which the children had acquired HIV.

PATIENTS AND METHODS

Evaluation Process

All children seen by the AIDS team who presented with or developed indications of possible abuse or neglect were referred to the child protection team for evaluation. Data for this study were collected at the time of the assessment of each child and represent cumulative information regarding the child's environment from the family, child, child protection team, AIDS team, social service agencies, schools, and, often, charitable agencies. Child sexual abuse was defined in 1977 as the involvement of dependent developmentally immature children and adolescents in sexual activities that they do not fully comprehend, to which they are unable to give informed consent, or that violate the social taboos of family roles.¹ Child sexual abuse includes rape, pedophilia, child prostitution, child pornography, child sex rings, and incest.

Multiple issues often led to referral to the child protection team. The instigating events included (1) the suspicion of or disclosure of CSA volunteered by the child or a caretaker ($n=2$); (2) abnormal genital findings revealed by routine medical examination ($n=5$); (3) suspected physical abuse or neglect, or a chaotic family environment ($n=3$); (4) medical or behavioral histories indicative of CSA ($n=5$); (5) children older than 6 years at onset of HIV disease, or with no known risk factor for HIV ($n=3$); and (6) the child was an HIV-positive sibling of a sexually abused child ($n=1$). All of the children were known to be infected with HIV prior to the diagnosis of CSA.

Evaluation for CSA

The evaluation of a child for CSA began with a family interview regarding the family constellation, patterns of care for the child, interactions of family members, behavioral characteristics of the child, and concerns or knowledge that the caretaker may have had regarding possibly abusive events. The following five groups of data needed for adequate evaluation of possible CSA were then obtained: (1) a review of the behavioral history of the child; (2) a review of the medical history of the child; (3) diagnostic interview(s) with the child; (4) results of physical examination; and (5) assessment for other sexually transmitted diseases.²⁻⁴

The diagnostic interviews followed a standard format. Draw-

Accepted for publication November 6, 1990.

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Presented in part at the annual meeting of the Society for Pediatric Research, Anaheim, Calif, May 11, 1990.

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ings and anatomically correct dolls were available for use when appropriate.⁵ In the present study, "disclosure" refers to the disclosure by the child or witness of a specific sexually abusive act. Perpetrators were "identified" if the child or a caretaker had specifically identified the person as an assailant. Perpetrators were considered "suspected" if the interview or historical information indicated sexually inappropriate interactions with the study child or another child and unsupervised access to the study child.

Each child received a complete physical examination and external genital examination using standard techniques.^{6,7} For the girls, genital examinations included identification of hymenal type and contour, measurement of the horizontal diameter of the hymenal opening, and anal examination.^{8,9} Samples of vaginal secretions were examined for indicators of bacterial vaginosis and *Trichomonas*. Cultures of the introitus or vaginal canal of girls and of the anus of boys for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* were taken unless the child was receiving antimicrobial therapy. Cultures of other sites and assessments for other infectious diseases were made when indicated.

Sexual abuse was confirmed if there was a detailed account from the child or a witness, a sexually transmitted disease in addition to HIV was found, the genital examination showed abnormal findings clearly indicative of abuse as defined at the 1985 National Child Sexual Abuse Summit meeting¹⁰ and subsequently updated,^{2,11,12} serial genital examinations showed significant changes, or the abuse was acknowledged by the perpetrator.

Mode of Acquisition of HIV by Study Children

The five possible routes of transmission of HIV that were separately assessed for each child were vertical transmission, transfusion, clotting factor concentrates, intravenous drugs, and sexual abuse (including child prostitution).

Data regarding vertical transmission included date(s) and result(s) of maternal HIV serologic tests relative to the birth of the child or HIV-related illness of the child. Data regarding transfusion-transmitted HIV included dates of transfusion to the child and the results of retrospective blood-bank HIV surveillance. None of the children in the study had received clotting factor concentrate therapy or had engaged in intravenous drug abuse. Data regarding transmission by sexual abuse included available information on the HIV status of the perpetrator(s) and the type of abuse.

Since many of the abused children had multiple possible modes of acquisition of HIV, the influence of each on the transmission of the HIV infection was stratified into categories of "proven," "possible," "disproven," and "unknown."

The following criteria were used to define the categories for vertical transmission: proven, the mother was HIV positive prior to or within 6 months of giving birth, or was first shown to be HIV positive 6 or more months after delivery and the child had an opportunistic infection or lymphocytic interstitial pneumonia by the age of 2 years; possible, the mother was first known to be HIV positive 6 or more months after delivery; disproven, the mother was HIV negative 6 or more months after delivery; and unknown, the mother's HIV seroactivity was unknown.

Criteria to define the categories for transmission by transfusion were as follows: proven, the mother was HIV negative at or after delivery and the child was known to have received an HIV-contaminated transfusion; possible, the mother was first known to be HIV positive 6 or more months after delivery and the child received an HIV positive transfusion; disproven, the child either received no transfusion, or it was HIV negative; and unknown, the child received a transfusion and retrospective surveillance was not able to trace the unit.

The criteria to define the categories for transmission of HIV through CSA were as follows: proven, either all other risk factors were disproven or the child was older than 12 years when HIV was first diagnosed, sexual contact had involved high risk for HIV, and no other factor had been proven; possible, the perpetrator was either HIV positive or unknown, and no other risk factor was proven; disproven, identified perpetrator was HIV negative; and unknown: an additional risk factor was proven. Inclusion in this report required that sexual abuse of the child had

Table 1.—Forms of Child Sexual Abuse

	Female Children (n = 11)	Male Children (n = 3)
Genital-vaginal	7	Not applicable
Digital-vaginal	2	Not applicable
Genital-rectal	4	1
Genital-oral	3	0
Unknown	4	2

been confirmed. A conservative definition of proven transmission of HIV by CSA gave priority to other known modes of transmission.

Sociological Setting

The social settings of the subjects were evaluated for five sociological risk factors for CSA identified from the 1987 National Survey of Children.¹³ In that study, a significantly greater incidence of CSA was experienced by girls who had lived apart from their biological parents before age 16 years; had been raised in poverty; had an emotional, physical, or mental handicap; and had family members who were alcoholic or drug abusers.

Other aspects of the social setting that were recorded in the present study included prostitution by adults in the home; the presence of multiple, unrelated, and frequently changing live-in visitors to the household; significant personality disorder of a caretaker; and AIDS encephalopathy or other AIDS-related disability of a caretaker.

RESULTS

Fourteen HIV-positive children were confirmed to have been sexually abused. The children included three boys and 11 girls (79% female) whose ages at the time of the diagnosis of CSA ranged from 3.5 to 13 years and whose mean age was 6.2 years. Thirteen of the 14 children were classified as P-2 based on Centers for Disease Control (CDC) criteria at the time they were diagnosed to be HIV positive. Eleven children were black, two were white, and one was Native American.

Diagnosis of CSA

Each of the 14 children with confirmed CSA either had disclosed sexual abuse, had genital or anal findings strongly indicative of CSA, or both. All of the 11 girls had abnormal examinations of the introital area and/or hymen. Two of the three boys had abnormal anal examination results. The genital findings indicative of abuse were scars or healed lesions of the posterior fourchette, (n = 4); scars, tears, notches, or significant distortions of the hymen (n = 5); recurrent or persistent vaginal discharge and odor or vaginal bleeding (n = 6); hymenal opening size greater than or equal to 8 mm in a prepubertal child or a significant change in the genital examination results on serial evaluations (n = 8); perianal scars (n = 2); significant and rapid anal dilation (n = 4); and perianal lesions (n = 1). Neither *N gonorrhoeae* nor *C trachomatis* was isolated from the vagina, throat, or rectum of any study child. Three children had a sexually associated disease other than HIV; two had bacterial vaginosis¹⁴; and one had condylomata acuminata.¹⁵

Eight children were able to disclose their abuse. Two made partial disclosure and four were unable to disclose. The forms of sexual abuse described by the eight children who were able to disclose are listed in Table 1.

All identified or suspected perpetrators were male. The number of known or suspected assailants and their relationship to the child when information was available are

Table 2.—Relation of Identified and Suspected Perpetrator(s) to an Assaulted Child

Relation	No. Identified	No. Suspected
Brother	1*	...
Father	1	3
Uncle	2	1*
Grandfather	2*	...
Foster father	1*	...
Foster brother	1*	...
Nonrelated assailant of child prostitute	7*	...

*One of multiple identified or suspected assailants of a single child.

Table 3.—Assessed Mode of Acquisition of Human Immunodeficiency Virus in Sexually Abused Children (n = 14)*

Mode of Acquisition	Proven	Possible	Disproven	Unknown
Child sexual abuse	4	6	...	4
Vertical transmission	3	5	5	1
Transfusion	2	...	12	...

*Acquisition of human immunodeficiency virus by clotting factor concentrate and by intravenous drug use was disproven in all cases.

shown in Table 2. For four children, the number and identity of perpetrator(s) was unknown. A single perpetrator was identified for three children, and for three children multiple perpetrators were identified. For two children a single perpetrator was suspected. For one child, one perpetrator was identified and additional perpetrators were also suspected. For another child, one perpetrator was suspected while the multiple perpetrators known to have abused the child were unidentified.

Acquisition of HIV

Using the criteria stated in the "Patients and Methods" section, an assessment was made of the mode of transmission of HIV when all data were considered. The results are shown in Table 3. For four (29%) of the 14 children, CSA was the only means of transmission of HIV to the child. A brief synopsis of the histories of these children follows. To protect the identities of the children, gender identification is not provided.

CASE 1.—The child was an emotionally abused, physically healthy child who lived in fear of the stepfather. At age 13 years, the child ran away from home and lived as a child prostitute for 3 months, during which time sexual practices included unprotected anal-receptive intercourse with multiple high-risk adults. Intravenous drugs were never used. The child had never had a transfusion and was not hemophilic. The mother was not tested but had no risk factors for HIV. At age 15 years, the child requested an HIV assay because of the high-risk history. Results of enzyme-linked immunosorbent assay (ELISA) and Western blot were positive, and the disease was CDC class P-1, subclass B. It was concluded that the child had acquired HIV as a child prostitute.

CASE 2.—At age 3 years 9 months, this child was HIV positive based on ELISA and Western blot test results; the disease was CDC class P-2, subclass A. The child's mother was HIV negative. The child had not received a transfu-

sion or blood products and was not hemophilic. Genital examination results were abnormal and included condyloma acuminatum, which had first been noted at age 3 years and 3 months. After partial disclosure it was concluded that the abuse had occurred during a chaotic family episode when numerous caretakers had had access to the child, and that the child had acquired HIV during the abuse.

CASE 3.—This child was aged 2 years 2 months when diagnosed to be HIV positive by ELISA and confirmed by Western blot; the disease was CDC class P-2, subclass F. The mother was HIV negative by ELISA, Western blot, and HIV culture. Although the child had received a transfusion, the donor was HIV negative. The child was not hemophilic. Genital examination was positive for traumatic abuse. Although verbal disclosure was obtained, identification of the assailant was not made, and a suspected assailant refused HIV testing. Because of the disclosure and the fact that another child had been sexually abused in the same home, the child was removed from the household and restricted from contact with the suspected perpetrator. Further abuse was subsequently documented by the development of new physical signs and symptoms, but specific identification of the perpetrator again could not be made. It was concluded that the child had acquired HIV during abuse by multiple perpetrators.

CASE 4.—This child was diagnosed at age 6 years and 2 months to be HIV positive by ELISA and Western blot, and classified as CDC P-2 subclass C. At the time of the diagnosis, the mother was HIV-negative, the child had never had a transfusion, and the child was not hemophilic. The genital examination revealed definitive evidence of traumatic abuse, as did the medical history. Two assailants were identified, one of whom was known to be HIV positive. It was concluded that the child had acquired HIV infection during child sexual abuse by an HIV-positive assailant.

Knowledge by the Assailant of the Possibility of HIV Transmission to or From the Child

Three of the assailants who were identified or suspected were HIV positive and knew of their HIV status at the time they assaulted the child. There was no indication from the children that "safe sex" precautions had been taken.

Eight identified or suspected assailants were aware that the child was HIV positive at the time of the assault. Five of these eight were themselves either HIV negative or their status was unknown when the child was assaulted. Again, there was no indication from the children that "safe sex" precautions had been taken.

COMMENT

In a recent review of the data from the 1987 National Survey of Children, social settings were identified that increased the risk of CSA.¹³ All but one child in the present study had two or more of these risk factors, and the proportion of children who had a given risk factor ranged from 43% to 71%, as shown below.

Social Conditions	No. (%) of Children
Lived apart from both biological parents	6 (43)
Raised in poverty*	10 (71)
Child was handicapped†	9 (64)
Alcoholic family member*	7 (50)
Drug abusing family member*	10 (71)
Prostitution at home	4 (29)
Transient adults living at home	8 (57)
Mentally ill caretaker	5 (36)
AIDS-related disability of caretaker	2 (14)

*Risk factors for CSA identified by National Survey of Children.¹³
†Handicap was probably apparent before onset of CSA.

In the National Survey of Children, 6% of girls with no risk factor, 9% of girls with one risk factor, 26% of girls with two risk factors, and 68% of girls with three or more risk factors had been sexually abused as children. In the present study, five of these identified factors were assessed, and 11 (78%) of 14 children had three or more of these risk factors each, demonstrating that the living circumstances of the abused children in the present study included previously described indicators for increased risk of sexual abuse.

Many of the circumstances surrounding the sexual abuse of these children are also previously identified risk factors for adult HIV transmission. First, promiscuous sexual activity with multiple partners is a well-defined risk factor for adult HIV infection.¹⁶ In the present series, seven (50%) of 14 children were known or suspected to have been assaulted by multiple perpetrators, eight children (57%) lived in homes in which casual adult acquaintances frequently slept in the home, thereby creating opportunities to abuse a vulnerable child, and four of these eight homes were also the sites for prostitution by adult caretakers. One of the children in the study had turned to child prostitution, itself a form of CSA.¹⁷ A second risk factor for adult HIV infection is sexual contact that is physically traumatic or involves impaired mucosal barriers. Both anal-receptive and oral-receptive sex have been associated with increased rates of transmission of HIV in adults, and were acts that these children described.¹⁸⁻²⁰ Furthermore, the children in the study had an unusually high incidence of physical signs of genital injury compared with usual groups of sexually abused children. A third risk factor for adult HIV infection is sexual intercourse without barrier protection. Assailants of children in this study practiced high-risk and unprotected sex even when the assailant knew himself to be HIV infected or when he knew the child to be HIV infected. A fourth risk factor for adult HIV infection, which was also found in most children in the study, is genital mucosal lesions as evidenced by vaginal bleeding, discharge, infections, and scars, perianal infections, lesions, and scars, and other sexually transmitted diseases.²¹ Finally, the adult population with whom many children lived were at increased risk of HIV from the use of illicit drugs. Use of drugs and alcohol by caretakers may also have diminished their ability to protect the child and lowered their threshold for sexual aggression.^{22,23} Consequently, these children were subjected to forms of sexual intercourse that were known from adult studies to be especially hazardous regarding transmission of HIV, and the children lived in family and social settings in which many adults who were their caretakers were at increased risk of being HIV infected.

In spite of the multiple risk factors for CSA that characterize the lives of many children with HIV, acquisition of HIV by children through abusive sexual assault has been infrequently considered or reported in the medical literature. Although individual case reports have provided evidence that this route of transmission should be examined for children with HIV,^{24,25} few medical reviews of the routes of transmission of HIV or of unsolved epidemiologic problems with HIV allude to transmission through CSA.^{2,26-29} For example, the exposure categories for reporting cases of childhood HIV infection by the Centers for Disease Control do not include the category of exposure through sexual contact. The lack of data and the need for policies on the testing of abused children for HIV has been the subject of a recent review.³⁰ The present study indicates that at least four (4.2%) of 96 children with HIV and four (29%) of 14 sexually abused children with HIV

acquired the infection through CSA. These represent the minimal percentages of pediatric HIV disease that can be attributed to CSA, since the abused children were identified during standard, nondirected pediatric interactions rather than by specific screening for abuse. In addition, children who also had other "possible" modes of transmission, such as maternal HIV, could not be proven to have acquired their disease through CSA. It was notable that four of the five children for whom vertical transmission of HIV was assessed to have been "possible" because the mother was HIV positive were older than 3 years when AIDS-like illness first began. This would be a long incubation period for perinatally transmitted HIV,³¹ and some of these children may instead have acquired their disease through CSA. This situation is exemplified by one of the study cases, in which the HIV-positive man who was identified as the perpetrator of a child's abuse was also the source of the mother's HIV infection.

The diagnosis of CSA in children who have AIDS or who are in a high-risk environment is of particular importance because some immediate and delayed behavioral sequelae of CSA may put the adolescent and adult survivor at increased risk of exposure to HIV or transmission of HIV to others if they are infected. First, high-risk sexual behaviors that may characterize female survivors of CSA include early entry into sexual activities, sexual promiscuity, and a particular vulnerability to further abuse and sexual exploitation, including prostitution and unintended pregnancy at an early age.³²⁻⁴⁰ Male victims of CSA may develop a cycle of sexual behavior in which the child victim becomes a sexual aggressor of other children, either immediately or in adulthood.⁴¹ Multiple victims may be involved.⁴² The consequences of the intersection of child sexual abuse with immediate and delayed risk factors for acquisition of HIV are dramatically highlighted in the "street" children of New York, NY.⁴³ Many of these children were sexually abused in earlier childhood, presumably providing their motivation for leaving their homes at a highly vulnerable, adolescent age.

In conclusion, this study has demonstrated that child sexual abuse was the proven mode of transmission in at least 4% of all study children with HIV followed up by the pediatric AIDS team, and may have been the mode of transmission for a considerably larger proportion of cases. The abused children lived in circumstances that put them at high risk for both CSA and HIV infection, and these risk factors often overlapped. Assailants were known to have abused children in spite of knowing themselves or the child to be HIV positive. Prevention of HIV transmission in populations of children and adolescents cannot be successful without the development of policies and resources to identify and eliminate the underlying sexual abuse to which these children are exposed. Sexual abuse and its consequences provide a major mechanism for the introduction of HIV to children and adolescents.

We are grateful for funding from the National Institutes of Allergy and Infectious Disease for the Duke University Pediatric AIDS Treatment and Evaluation Unit, Durham, NC.

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Sexual Maturation and Blood Pressure Levels of a Biracial Sample of Girls

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• A cross-sectional survey of 142 black and 361 white girls was performed to investigate whether differences in the timing of maturation account for blood pressure differences between same-aged subjects. Data were collected on blood pressure, anthropometric parameters, socioeconomic status, and secondary sex characteristics. Analysis of covariance was used to determine whether blood pressure for black and white girls differed significantly after adjusting for the confounding effects of different body size and sexual maturation distributions of the two groups. Advanced sexual maturation of the black girls contributed as much as the larger body sizes of the black girls to the blood pressure differences found between the black and white girls. Assessment of an individual's stage of sexual maturation at blood pressure measurement should be considered as important as the measurement of height and weight.

(AJDC. 1991;145:142-147)

The underlying mechanism of the development of blood pressure level during childhood and adolescence is unknown. This is due, in part, to the many physical, physiological, and hormonal changes; the variability between and within individuals and populations of the onset and rate of sexual maturation; and the rate of growth that occurs during childhood and adolescence.

The association of height and weight with blood pressure during childhood has been well documented.^{1,2} As a result of those findings, the Second Task Force on Blood Pressure Control in Children³ revised its recommendations from its first report⁴ to include consideration of the child's height and weight at the measurement of blood pressure. However, an important variable not considered or evaluated for those blood pressure standards was sexual maturation. Many of the data sets used for the task force report did not have data available on sexual maturation, preventing its inclusion in the analyses. The current second task force age- and sex-specific blood pressure standards, however, include adolescents in various stages of sexual maturation. This variability in maturation possibly obscures the isolated effect of puberty on blood pressure level.

A number of studies on blood pressure and sexual maturation have produced conflicting results.^{5,6} Londe et al⁶

concluded from their study of 189 measurements among girls 10 to 14 years of age that there is no relationship between blood pressure level and sexual maturation. The authors based their findings, however, on single determinations of the cyclic luteinizing and follicle-stimulating hormones. The daily intraindividual variation of these hormones precludes their use as cross-sectional, single-determination, independent variables. The authors did not control for possible confounding effects or covariance. They also seemed to misunderstand the strength of longitudinal studies for the investigation of development, as evidenced by their statement, "since blood pressure increases with age, longitudinal studies are unsatisfactory, because rise in pressure may be due to age rather than sexual maturation."

It is not known whether sexual maturation contributes to blood pressure during childhood and adolescence independently of chronological age or body size. Thus, it is logical to compare blood pressure levels of two groups that have different ages of onset of and, possibly, different rates of sexual maturation. A more sexually mature population would be expected to have a higher mean blood pressure than a comparison population of the same chronological age but sexually less mature. Black youths are known to enter into puberty at a younger chronological age than white youths.⁷

The objective of this study was to investigate whether differences in the timing of maturation account for blood pressure differences between same-aged black and white girls. Specifically, this study analyzed the data to answer the following questions: (1) Are there differences in systolic and diastolic blood pressure between black and white girls? (2) Are there differences in height, weight, body-mass index, socioeconomic status, and timing of sexual maturation between black and white girls? (3) Are observed patterns of differences in blood pressure associated with differences in height, weight, body-mass index, socioeconomic status, and timing of sexual maturation?

SUBJECTS AND METHODS

Participants were recruited from female students enrolled in a public school district in central Texas for a cross-sectional study of blood pressure and maturation. The school district was large, so schools were selected using a multistage sampling method with initial stratification of schools according to the enrolled students' socioeconomic status. A census tract for each eligible student was determined using the student's address. The median income levels associated with eligible students' census tracts, as

Accepted for publication October 26, 1990.

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Table 1.—Sociodemographic Characteristics of the Study Population

	Race, No. (%)	
	Black	White
Age category, y*		
7-9	59 (41.5)	123 (34.1)
10-12	47 (33.1)	160 (44.3)
13-15	27 (19.0)	67 (18.6)
16-18	9 (6.3)	11 (3.0)
Median income index†		
1	6 (4.4)	58 (16.3)
2	62 (45.9)	192 (54.1)
3	29 (21.5)	46 (13.0)
4	18 (13.3)	34 (9.6)
5	20 (14.8)	25 (7.0)

*The age distribution did not differ significantly between the races.

†The median income index, derived from the US Census, was missing for seven black and six white girls. $\chi^2 = 22.40$, $df = 4$, $P = .0001$.

Table 2.—Distribution of Secondary Sex Characteristics by Race

Stage	Secondary Sex Characteristics, %			
	Breast*		Pubic Hair†	
	Black	White	Black	White
1	22	22	21	34
2	16	26	15	19
3	23	24	15	16
4	25	22	37	22
5	14	6	12	9

* $\chi^2 = 14.97$, $df = 4$, $P = .005$.

† $\chi^2 = 15.63$, $df = 4$, $P = .004$.

published by the US Census Bureau, were combined and averaged to determine a representative median income level for each school.

The schools were categorized into four income level groups, from low to high. Four elementary schools (grades 2 through 5), two middle schools (grades 6 through 8), and the health classes from two high schools (grades 9 through 12) were randomly selected. Students from these selected schools volunteered for participation in this study.

Informed consent and assent were obtained from the parent or guardian and student, respectively. This project was approved by the institutional review board of the University of Texas Health Science Center, Houston.

Sample size calculations were done to determine the number of black and white girls necessary to detect a minimum difference in mean blood pressure levels of 4 mm Hg. With an α level of .05 and 90% power, a minimum of 118 girls in each racial group was required.

The highest participation rate occurred in the elementary schools (63%) and the lowest rate occurred in the high schools (16%). Hence, this was largely a study of the younger age groups. To examine possible nonresponse bias, addresses of the nonresponders were abstracted from official school records. The addresses were categorized by census tract and rank-ordered by the socioeconomic level of the census tract. The socioeconomic status distribution did not differ between responders and nonresponders. In addition, the ethnic group distribution of the responders was similar to that of the nonresponders. There appeared to be no biases that would cause serious concerns when studying the relationship of blood pressure and the characteristics of the study population.

The subject's upper-arm circumference was measured with a steel tape to select a cuff of appropriate bladder width, ie, a cuff with a bladder that could completely encircle the circumference of the arm. The same trained and certified observer performed blood pressure measurements on the right arm of all subjects after they had been seated for approximately 5 minutes. A standard desktop mercury sphygmomanometer (Baumanometer, W. A. Baum Co Inc, Copiague, NY) was used to measure the systolic and fourth- and fifth-phase diastolic blood pressures. Three measurements were performed; the last two were averaged and used in the analyses.

Trained observers followed standard methods for the anthropometric measurements.⁸ Height was measured with the subject wearing no shoes, standing with arms at sides, legs straight, feet together (toes and heels), knees together, eyes looking straight ahead, and shoulders, buttocks, and heels against a steel tape firmly attached to a wall. The zero mark of the tape was placed at foot level.

The edge of a plastic right angle was placed on the top of a subject's head to form a 90° angle with the wall. The measurement was read to the nearest millimeter. Weight was measured on a beam balance scale. Without shoes and in light clothing, the subject stood still in the middle of the platform. The observer first moved the biggest balance weight, then the smaller upper balance, until the indicator on the balance stabilized at zero. The measurement was read to the nearest 0.1 kg. The scale was calibrated each day with dead weights matching the expected weights of the participants. The body-mass index (kg/m^2) was calculated on the basis of the height and weight measurements. The ratio of weight to the square of height was used to estimate total body fat.⁹

To determine the stage of sexual development as described by Tanner,¹⁰ each subject self-assessed her secondary sex characteristics according to drawings of the breast and pubic hair maturation stages.¹¹ Pearson correlation coefficients of 0.63 and 0.81 for breast and pubic hair stages, respectively, were reported by Morris and Udry¹¹ from a validity study of the self-assessment method. Their study population consisted of 12- to 16-year-olds. Frankowski et al¹² investigated the ability of children aged 7 through 12 years to perform self-assessment from drawings of the maturation stages. There was a strong correlation with physician ratings for breast stage ($r = .75$) and pubic hair stage ($r = .88$). Because of the success of the self-assessment method in these studies, it was used in the current study.

Smoking history, menstrual history, and oral contraceptive use were obtained from each participant during a standard interview with a research assistant. All items were close-ended.

Subject and parental health histories, subject medication use, and parental education and occupation were collected by means of a questionnaire that was mailed, with instructions for completion, to the parents of each subject. All questions were close-ended. Whether the mother, father, or both parents completed the interview was not determined.

Comparisons of blood pressure, height, weight, and body-mass index between the black and white girls were based on two-tailed t tests. The χ^2 test was used to compare the distributions of socioeconomic status and sexual maturation between the two race groups. Analysis of covariance was used to compare the mean blood pressure levels of the black and white girls, adjusting for possible confounding effects due to differing independent variable distributions in the two groups. Because misleading results can be obtained if inappropriate variables are used to adjust blood pressure differences between groups, only variables that were significantly associated with the dependent variable, systolic or diastolic blood pressure, were included as covariates in the analysis.

RESULTS

Race Differences in Socioeconomic Status, Anthropometric Parameters, and Sexual Maturation

The study population comprised 142 black girls and 361 white girls (Table 1). The mean age of the black girls (10.6 ± 2.7 years) did not differ from that of the white girls

Table 3.—Median Ages at Entry to Sexual Maturation Stages		
	Median Age by Race, y	
	Black	White
Breast stage		
2	8.47	9.28
3	9.65	11.00
4	11.85	12.91
Pubic hair stage		
2	8.36	9.69
3	9.51	11.25
4	10.71	12.61

(10.7±2.3 years). There was, however, a significant difference in the socioeconomic status distributions. The majority of the white girls were in the top two socioeconomic status categories, whereas the majority of the black girls were in the second and third socioeconomic status categories. However, in a univariate regression analysis of socioeconomic status and blood pressure, socioeconomic status was not significantly associated with systolic or diastolic blood pressure.

The black girls were significantly taller (by an average of 6 cm) and heavier (by an average of 6 kg) than the white girls at ages 7, 9, and 12 years and significantly taller (but not heavier) at ages 10 and 14 years. The body-mass index was used as an indicator of body fat. Body mass did not differ between the black and white girls at any age.

A significantly larger percentage of the black girls were at the more advanced stages (Tanner stages 4 and 5) of sexual maturation than the white girls (Table 2). For breast stage, 39% of the black girls were at either stage 4 or 5 compared with 28% of the white girls. For pubic hair stage, 49% of the black girls were at either stage 4 or 5 compared with 31% of the white girls.

The Spearman-Kärber procedure was used in a manner similar to that of Villarreal et al¹³ to estimate the median age at entry into the breast and pubic hair stages. This procedure allows the use of cross-sectional data. Black girls had younger median ages of entry into all stages compared with white girls (Table 3).

All girls were questioned about their menstrual status. A larger percentage of the black girls (36%) had reached menarche than the white girls (24%, $P<.01$), even though the age distributions and mean ages were the same.

Race Differences in Blood Pressure

Table 4 presents the mean (SD) systolic and diastolic blood pressures for participants classified by racial group and age. Black girls had higher mean systolic and diastolic blood pressures than white girls in every age category. These differences were statistically significant only in the 10- to 12-year-old age category. However, the 95% confidence intervals around the differences in mean blood pressure between the black and white girls for the age categories of 7 through 9 and 13 through 15 years were close to not including the null value.

The unadjusted means for systolic and fourth- and fifth-phase diastolic blood pressure differed significantly between the black and white girls (Table 5). Fourth-phase diastolic blood pressures were compared for the girls less than 13 years of age in accordance with the recommendations of the Second Task Force on Blood Pressure Control in Children.³ As indicated by the 95% confidence intervals, the mean

Table 4.—Mean Blood Pressure by Race and Age				
Age Category, y	Blood Pressure, mm Hg			Difference Between Means (95% Confidence Interval)
	Race			
	White	Black		
Systolic				
7-9	100.3 (7.86)	98.1 (8.87)	2.2 (−0.52 to 4.92)	
10-12	108.1 (11.21)	102.7 (9.86)	5.4 (2.01 to 8.78)	
13-15	113.3 (9.64)	109.4 (9.67)	3.9 (−0.50 to 8.30)	
16-18	113.4 (9.54)	111.6 (10.59)	1.8 (−7.33 to 10.93)	
Fourth-Phase Diastolic				
7-9	66.0 (6.66)	64.1 (6.89)	1.9 (−0.26 to 4.06)	
10-12	71.9 (6.93)	68.1 (6.16)	3.8 (1.69 to 5.91)	
Fifth-Phase Diastolic				
13-15	69.9 (6.92)	67.2 (7.02)	2.7 (−0.49 to 5.89)	
16-18	74.2 (7.81)	69.8 (5.90)	4.4 (−1.74 to 10.54)	

*Values are mean (SD).

blood pressure differences ranged between 1.4 and 5.6 mm Hg. The mean levels of the black girls were significantly higher than the mean levels of the white girls.

Race Differences in Adjusted Blood Pressure

Height, weight, and maturation stage were included in analysis of covariance models to test the differences in blood pressure between the black and white girls. The mean systolic and diastolic blood pressures for each ethnic group, unadjusted and adjusted for each covariate, are shown in Table 6. Correcting for the covariates of height, weight, or pubic hair stage did not change the pattern of differences in blood pressure between the black and white groups. The mean blood pressure remained higher for the black girls than the white girls, but the differences were no longer significant. Adjusting for sexual maturation (pubic hair or breast stage) produced results similar to those after adjusting for body size (height or weight).

COMMENT

This study examined blood pressure levels and the timing of sexual maturation among young black and white female participants in a cross-sectional survey. At the time of the survey, same-aged black girls were more sexually mature than white girls. The black girls also had entered each stage of breast development and pubic hair growth at a younger median age. Black participants had higher mean systolic and diastolic blood pressure levels in all age categories and as a group. Adjustment for body size, represented by height or weight, and adjustment for sexual maturation, represented by secondary sex characteristics, equally reduced the blood pressure differences. Thus, the stage of sexual maturation may play a significant role in the assessment of blood pressure level during adolescence. Recording the stage of sexual maturation of a subject at blood pressure measurement may be as important as recording height and weight.

Sexual maturation is a complex process represented by many physical, physiologic, and hormonal changes, some of which could be related to blood pressure patterns. Because body size, represented by height and/or weight, is highly correlated with the stage of maturation, it is difficult

Table 5.—Differences in Unadjusted Mean Blood Pressure Between Black and White Girls

	Blood Pressure, mm Hg		
	Race*		Difference Between Means (95% Confidence Interval)
	Black	White	
Systolic	106.2	102.7	3.5 (1.4 to 5.6)
Fourth-phase diastolic	70.4	67.5	2.9 (1.5 to 4.4)
Fifth-phase diastolic	66.0	63.1	2.9 (1.4 to 4.6)

*Values are means.

Table 6.—Mean Blood Pressure Adjusted by Covariates

	Blood Pressure by Race, mm Hg*	
	Black	White
Systolic		
Unadjusted	106.18	102.67
Adjusted by Weight	105.12 ± 0.71	103.09 ± 0.44
Height	105.08 ± 0.75	103.10 ± 0.47
Pubic hair†	105.00 ± 0.81	103.14 ± 0.50
Fourth-Phase Diastolic		
Unadjusted	70.41	67.50
Adjusted by Weight	69.79 ± 0.53	67.75 ± 0.33
Height	69.71 ± 0.53	67.78 ± 0.33
Pubic hair†	69.61 ± 0.56	67.81 ± 0.35
Fifth-Phase Diastolic		
Unadjusted	66.04	63.15
Adjusted by Weight	65.44 ± 0.57	63.38 ± 0.36
Height	65.34 ± 0.56	63.42 ± 0.36
Pubic hair†	65.25 ± 0.59	63.46 ± 0.37

*Values are mean ± SD.

†Similar results were generated when breast stage was entered into the model.

to separate these two effects on blood pressure.¹⁴ However, analysis of covariance suggested that their individual effects on blood pressure were similar.

This study was large enough to guard against chance alone being responsible for the differences in mean blood pressure level between the black and white girls. However, the girls in this study may not be representative of a same-aged sample of girls from the US population; thus, the results may not be generalizable to the US population.

The use of the self-assessment method for estimating sexual maturation may be questioned by some. However, several studies have demonstrated that this is a valid method for the assessment of sexual maturation.^{11,12} Also, it does not seem reasonable that the black girls would systematically report a higher stage of sexual maturation than the white girls. The median age of entry to each stage linearly increased with chronological age for both the black and white girls; this supports the biologic plausibility of the method.

Additional potential confounding variables not considered in this study were nutritional status and physical ac-

tivity and fitness of the girls. A confounding variable is a factor associated with both the dependent and independent variables under study. Undernutrition has been reported to be associated with the rate of maturation; however, its association with blood pressure level is unknown. There are data regarding diet composition and blood pressure level; however, the relationship of diet with sexual maturation is unknown. Reliable methods of recording diets during childhood and adolescence are still being developed, so data are difficult to collect. Accurate methods of recording physical activity and fitness during childhood and adolescence are also still being developed. Perhaps the results of and methods developed for the Childhood and Adolescence Trial of Cardiovascular Health, funded by the National Heart, Lung, and Blood Institute at four US field centers, will provide us with reliable and valid methods for assessing cardiovascular risk factors during childhood and adolescence.

Because of the cross-sectional design of this study, it could not be determined whether a difference in the rate of puberty of the black girls compared with the white girls had an influence on the blood pressure level. A longitudinal design would be necessary to observe the rate of maturation. There are, however, no current longitudinal studies that observe rates of sexual maturation by race.

Inherent metabolic differences in maturation between ethnic groups may account for the differences in mean blood pressure level. Perhaps the onset of sexual maturation at an earlier age in black girls produces a more striking blood pressure response than the onset of sexual maturation at a later age in white girls. However, remarkably little is known about the anthropometric and physiologic correlates of sex hormones and the possible effects of increased hormone production during adolescence on blood pressure for either black or white girls. In the United States, the prevalence of essential hypertension in adults is considerably higher among blacks than whites.¹⁵

Investigating the blood pressure levels of two groups of girls with a different distribution of sexual maturation stages led to the conclusion that the stage of sexual maturation should be taken into consideration at routine blood pressure measurements. Early maturers could be at a higher risk of hypertension as adults.

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BOOK REVIEW

Fasting Girls: The History of Anorexia Nervosa

By Joan Jacobs Brumberg, 370 pp, with illus, \$9.95, New York, NY, A Plume Book, New American Library, Division of Penguin Books USA, 1989.

Students of anorexia nervosa and those responsible for treating patients with eating disorders continue to struggle with the question of the cause of this biopsychosocial condition. Perhaps out of frustration and the inherent management difficulties many physicians are quick to embrace the concept of a biologic vulnerability as the organic cause of the disorder. While not dismissing the importance of biologic determinants and the possibility that anorexia nervosa may be a manifestation of an underlying hypothalamic defect, Brumberg builds a convincing case against this simplistic biomedical model. As physicians, we would very much welcome a breakthrough proving that the unusual eating behaviors of patients with eating disorders are somehow the result of an imbalance, deviance, or abnormality of biological processes. If such were the case, it might be prevented by a vaccine for those with a strong family history of eating disorders or treated with a specific hormone or chemical that quickly would alleviate the problem, much like that used for schizophrenia and bipolar and depressive disorders. Stressing the sociocultural influences on the development of anorexia nervosa, the author argues for a multifactorial and asks why, if the cause is primarily organic, there is a predominance of the condition in middle and upper social class women, and why recently there has been an increase in the incidence of this and other eating disorders. Brumberg forced me to reconsider my bias toward accepting the easy answer of biologic predisposition or vulnerability.

In Western society, fasting and

purging have been an important part of Judeo-Christian religious practices. In *Fasting Girls* the author traces the history of food refusal from the medieval period, when between 1200 and 1500 the practice was considered to be a characteristic of medieval spirituality. A discussion of female saints, for whom fasting was basic to the model of female holiness, is presented in an early chapter. The emphasis, however, is on the "fasting girls" of the 19th and 20th centuries and the heated debate between physicians on the one side and religious leaders and spiritualists on the other. Increasingly, scientifically minded physicians objected to the idea of a miraculously inspired loss of appetite (anorexia mirabilis). According to Brumberg, "Among certain segments of the Victorian religious community, fasting girls and the fiction of total food abstinence became a way of sustaining belief itself." The 19th-century Victorian family, with its rigidity and possessiveness and its use of food as a reward and punishment, is identified as a major determinant of modern-day anorexia nervosa. In the case of anorexia mirabilis ("holy anorexia"), the quest for purity through self-sacrifice and the belief that there are other forms of sustenance, such as prayer and the Christian Eucharist, provided the driving force for fasting. In making a case that the self-imposed starvation of the saints and of 19th- and 20th-century adolescent women took place under different conditions, the author underscores her belief that to a great extent cultural factors determine the manifestations of this illness.

A fascinating chapter deals with the history of anorexia nervosa and its early introduction into the medical literature. In 1694 Richard Morton, in *Phthisologia; or, a Treatise on Consumptions*, described two cases of "nervous consumption" considered by many to be the first reported cases of anorexia

nervosa. Brumberg challenged that assumption and introduced William Stout Chipley (1810 to 1880), who published in the *American Journal of Insanity* the first American description of sitomania, a "phase of insanity" characterized by an "intense dread of food." A discussion of institutionalized patients who rejected food is interesting, but most delightful is the close look at Sir William Withey Gull (1816-1890) who, in 1868 at the annual meeting of the British Medical Association, first made reference to the condition. A most prestigious consultant and physician to Queen Victoria and her family, he was held in high esteem. Nevertheless, it was a Paris neurologist, Charles Lasague (1816-1883), who preempted Gull's use of the term *anorexia* rather than *apepsia* (indigestion) and emphasized the importance of psychological and family factors, whereas Gull's approach was much more simplistic. The detailed description of the cases of Sarah Jacob, the "Welsh Fasting Girl," and Mollie Fancher, known as the "Brooklyn Enigma," and the raging controversy involving the "feisty" leading neurologists of the day, including William Hammond and George Beard, and eccentric believers (such as spiritualists), pious clergy, and physicians of "secondary status" are most informative and very fascinating.

Brumberg has a nice writing style, which makes it difficult to put the book down. She has made an important contribution to the history of medicine and psychology. It should be required reading for serious students of eating disorders and all those who are actively involved in their diagnosis and treatment.

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Lipoprotein Profiles in Hypercholesterolemic Children

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● Atherosclerosis is a process that begins in early life. Coronary heart disease is the result of complex interactions among a variety of risk factors of which hypercholesterolemia is but one. During routine screening, 500 children were identified with total cholesterol levels above the 95th percentile of 5.2 mmol/L (200 mg/dL). Lipoprotein profiles were then performed to confirm and delineate their lipid abnormalities. A definable lipid disorder was present in 85% of such children. Abnormal lipoprotein patterns included 292 children with type IIa, 99 with type IIb, and 25 with type IV phenotypes. An abnormally low high-density lipoprotein cholesterol level of less than 0.9 mmol/L (35 mg/dL) was observed in 20 children. Only 5% of patients were identified as being hypercholesterolemic because they had high-density lipoprotein cholesterol levels above the 95th percentile of 1.8 mmol/L (70 mg/dL). Thirty-two percent of children with total cholesterol levels above 5.2 mmol/L had a family member (sibling, parent, uncle, aunt, or grandparent) with a myocardial infarction prior to 55 years of age. Data from this study support universal cholesterol testing after 3 years of age and lipoprotein profiles for those with levels above 5.2 mmol/L.

(AJDC. 1991;145:147-150)

There is increasing evidence that routine cholesterol testing of children after 2 to 3 years of age is both appropriate and productive.¹⁻³ When a child is identified as having hypercholesterolemia, it is not uncommon to discover a lipid disorder in other family members. Increasing numbers of pediatricians are performing cholesterol screening at early ages,⁴ and they are more consistently advising patients and their families to avoid high-risk coronary life-style behaviors such as dietary excess, physical inactivity, and smoking.

A recent cholesterol surveillance study⁵ of 6500 children found nearly twice the expected number to have cholesterol levels above the Lipid Research Clinics' 90th percentile of 4.8 mmol/L (185 mg/dL).⁶ The present report concerns 500 children from the same study who had lipoprotein profiles performed because they had cholesterol levels above 5.2 mmol/L (200 mg/dL) detected by an earlier screening test. Recognizable types of lipoprotein abnormalities in this population of children and their lipoprotein profile data are presented.

PATIENTS AND METHODS

The private pediatric practice in which this study was carried out consists of six pediatricians and a pediatric nurse practitioner and is located in Parma Heights, Ohio. The children studied were at least 3 years old, white, and residents of southwest Cleveland suburbs. During routine health care visits, nonfasting total cholesterol levels were observed to be above 5.2 mmol/L (200 mg/dL). The original cholesterol screening was carried out on a fingerstick blood specimen using a reflectance photometer (Reflotron, Boehringer Mannheim Diagnostics, Indianapolis, Ind). An arbitrary decision was made, for purposes of this report, to study prospectively 500 consecutive children on whom lipoprotein profiles were then performed. Ninety percent of the studied population had lipoprotein profiles performed within 1 month of the original cholesterol screening test.

Lipoprotein samples were collected by venipuncture and analyzed with a Dupont Analyst instrument (Dupont Co, Wilmington, Del). Patients were scheduled for the procedure during early morning office hours after an overnight 12-hour fast. The instrument was calibrated daily according to manufacturer's recommendations and control serum samples were used regularly to check for precision and accuracy. Twice weekly, two trained office nurses performed the venipunctures and ran the lipoprotein profiles. The laboratory instrument is an automated microprocessor that photometrically measures the results of enzymatic cleavage of cholesterol ester and hydrolysis of triglycerides. Low-density lipoprotein (LDL) cholesterol was calculated using the standard formula⁷: LDL Cholesterol = Total Cholesterol - High-Density Lipoprotein Cholesterol (HDL) - Triglycerides/5.

The normal distribution of plasma lipid levels in children 3 to 19 years of age is shown in Table 1. The data are derived from the Lipid Research Clinics⁸ and the Bogalusa Heart Study.⁹ For purposes of this report, lipid levels above the 95th percentile and/or below the 5th percentile are defined as *abnormal*.

RESULTS

Five hundred children had lipoprotein profiles performed in the described pediatric office setting between August 1, 1986, and July 1, 1988. The mean age of the studied population was 8.1 years (range, 3 to 21 years), and the male-female ratio was 1:1 (251:249). Table 2 contains the descriptive statistics for the entire group of patients.

Figure 1 depicts the distribution of the 500 children according to important LDL cholesterol cutoff points as defined by the National Cholesterol Education Program for adults.¹⁰ Similar LDL cholesterol reference data and treatment recommendations for children are currently being considered by a panel of experts at the National Heart, Lung, and Blood Institute. Figures 2 through 5 are histograms showing the frequency distribution of LDL cholesterol, HDL cholesterol, and triglyceride levels for the 500 children who had lipoprotein analyses. The mean LDL-HDL ratio for the group was 2.9 (range, 0.9 to 9.5) compared with a normal value of 1.6 in a population of

Accepted for publication October 1, 1990.

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Table 1.—Expected Distribution of Serum Lipid Levels for Children 3 to 19 Years of Age*

Serum Lipid Levels	Distribution		
	5th Percentile	95th Percentile	Mean
TC	3.1	5.2	4.1
LDL-C	1.7	3.4	2.6
HDL-C	0.9	1.8	1.4
TG	0.4	1.3	0.9

*All values are in millimoles per liter. TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides.

Table 2.—Descriptive Statistics of 500 Hypercholesterolemic Children Whose Lipoprotein Profiles Were Tested*

Variable	Minimum	Maximum	Mean ± SD
Age, y	3	21	8.1 ± 4
TC	3.7	9.6	5.7 (220.9) ± 0.8 (29.9)
HDL	0.7	2.7	1.4 (54.4) ± 0.3 (12.7)
LDL	2.1	8.1	3.9 (149.4) ± 0.8 (30.3)
TG	0.3	5.6	1.1 (94.4) ± 0.6 (50.1)
LDL-HDL ratio	0.9	9.5	2.9 ± 1

*All lipid levels are in millimoles per liter. TC indicates total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and TG, triglycerides.

8000 school-age children in Bogalusa, La.¹¹

The frequency of recognizable abnormal lipoprotein patterns in these 500 patients based on the classification of hyperlipoproteinemia types described by Fredrickson et al¹² was as follows. There were 292 patients (58%) classified as type IIa with LDL levels higher than 3.4 mmol/L (130 mg/dL) and triglyceride levels higher than 1.3 mmol/L (110 mg/dL); 99 patients (20%) as type IIb with LDL levels higher than 3.4 mmol/L and triglyceride levels lower than 1.3 mmol/L; 25 patients (5%) as type IV with LDL levels lower than 3.4 mmol/L and triglyceride levels higher than 1.3 mmol/L; 20 (4%) as "low HDL" with HDL levels lower than 0.90 mmol/L (35 mg/dL), who were further divided into two groups of those with LDL levels higher than 3.4 mmol/L (n=13) and those with levels lower than 3.4 mmol/L (n=7). More information regarding lipid disorders in family members is required to make specific genotypic diagnoses. Familial hyperlipidemias may become evident as careful pedigrees are constructed for these children.

Twenty-three percent (n=116) of the children who originally had total cholesterol levels above the 95th percentile of 5.2 mmol/L (200 mg/dL) had LDL cholesterol levels lower than the 95th percentile of 3.4 mmol/L (130 mg/dL) when they had lipoprotein profiles performed. Fifty-six of the children whose total cholesterol levels were greater than 5.2 mmol/L had LDL cholesterol levels below the 95th percentile because they had high HDL cholesterol and/or triglyceride levels. Similarly, 60 children had LDL cholesterol levels below the 95th percentile because their total cholesterol levels had fallen below 5.2 mmol/L (Fig 6). Only 15 patients (3%) who had lipoprotein profiles performed were found to have total cholesterol levels lower

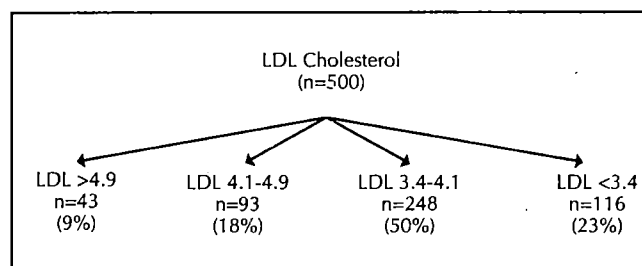


Fig 1.—Distribution of 500 hypercholesterolemic children who underwent a lipid profile test, according to low-density lipoprotein (LDL) cholesterol levels. All values are in micromoles per liter.

than the 75th percentile of 4.4 mmol/L (170 mg/dL).

COMMENT

Evidence is overwhelming that atherosclerosis begins early in life.¹³⁻¹⁵ Coronary artery disease results from complex interactions among various well-recognized risk factors, of which hypercholesterolemia is but one.¹⁶ Heredity (genetic disorders of lipoprotein metabolism) as well as environment (poor nutritional behaviors, sedentary lifestyle, and smoking) play important roles in the evolution of the disease process. Cholesterol surveillance in childhood allows the pediatrician to identify some, but not all, genetic disorders of lipid metabolism in early life. Not uncommonly, an identified hypercholesterolemic child serves as the index case to uncover a familial lipid disorder. For purposes of this report, the term *family member* includes siblings, parents, grandparents, aunts, and uncles.

Excessive dietary saturated fat and cholesterol, familial hypercholesterolemia, familial combined hyperlipidemia, and polygenic hypercholesterolemia can all be responsible for the isolated high levels of LDL cholesterol characteristic of type IIa hyperlipidemia. Type IIb hyperlipidemia is present when both LDL cholesterol and triglyceride levels are elevated and familial combined hyperlipidemia is the usual cause. Elevation of the triglyceride level alone characterizes the type IV phenotype that can be caused by familial hypertriglyceridemia, familial combined hyperlipidemia, or the nonfasting state. More complete family history and lipoprotein profile data are gradually being gathered from family members of these hypercholesterolemic children, and will enable genotypic classification, genetic counseling, and more specific treatment.

Accuracy and consistency of blood lipid measurements in the office setting have been issues of concern.¹⁷ There was remarkable agreement between cholesterol levels from one period to another in this group of patients despite using two different instruments to perform the test. Only 3% (n=15) of the population identified by routine screening had a normal cholesterol level (<75th percentile) at the time of subsequent lipoprotein analysis, and 93% had levels above the 90th percentile of 4.8 mmol/L (185 mg/dL). Similarly, 77% of children who were determined to be hypercholesterolemic by routine screening had LDL cholesterol levels above the 95th percentile, and only 2.5% had levels below the mean of 2.6 mmol/L (100 mg/dL). With careful attention to quality control, the instruments used for office lipid measurements have been shown to be 97% accurate.¹⁸ On the basis of office lipoprotein analyses alone, it is important to note that no treatment was provided for these children other than advice regarding diet and risk factor avoidance. Patients with more severe or complex hyperlipidemia and those for whom drug therapy became a consideration were candidates for referral to pediatric lipid clinics for evaluation and treatment. Children with LDL cholesterol levels above 4.1 mmol/L (160

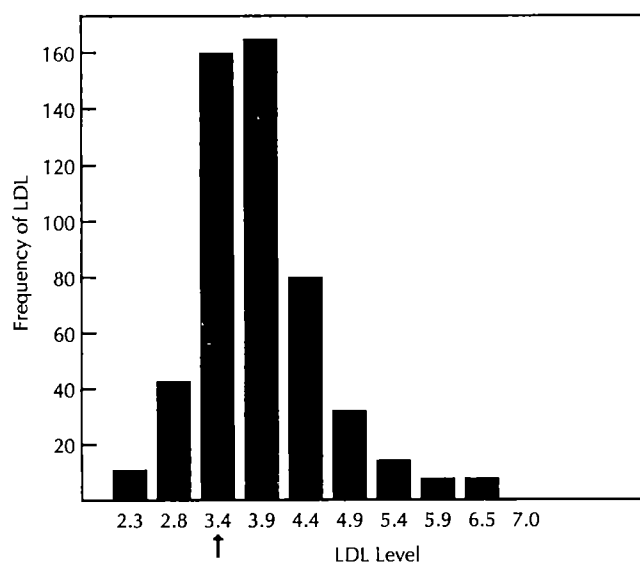


Fig 2.—Distribution of 500 patients according to low-density lipoprotein (LDL) cholesterol levels. Arrow indicates 95th percentile for age. All values are in micromoles per liter.

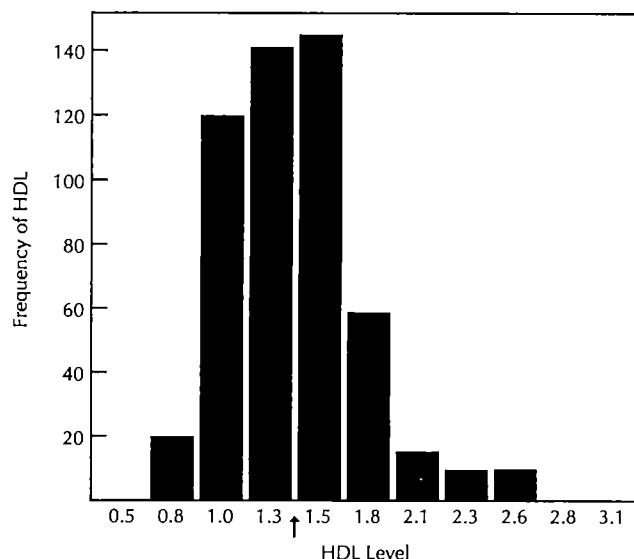


Fig 4.—Distribution of 500 patients according to high-density lipoprotein (HDL) cholesterol levels. Arrow indicates mean HDL cholesterol level. All values are in micromoles per liter.

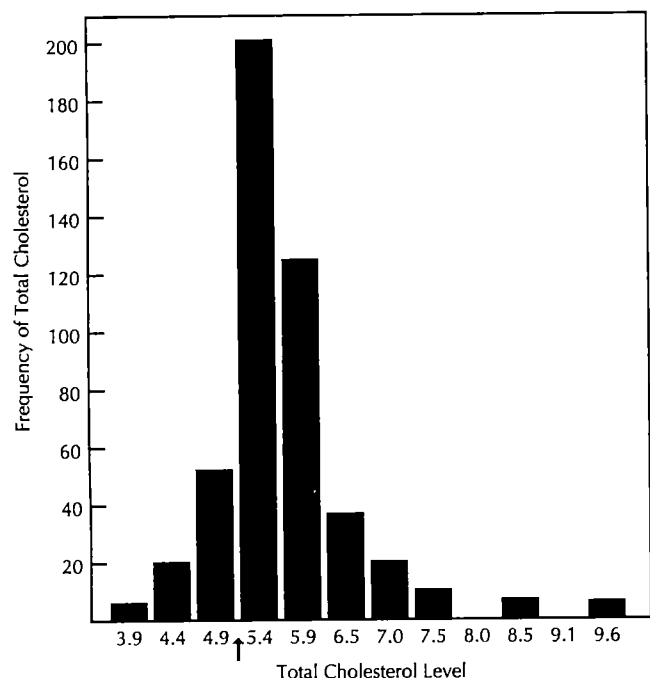


Fig 3.—Distribution of 500 patients according to total cholesterol levels. Arrow indicates 95th percentile for age. All values are in micromoles per liter.

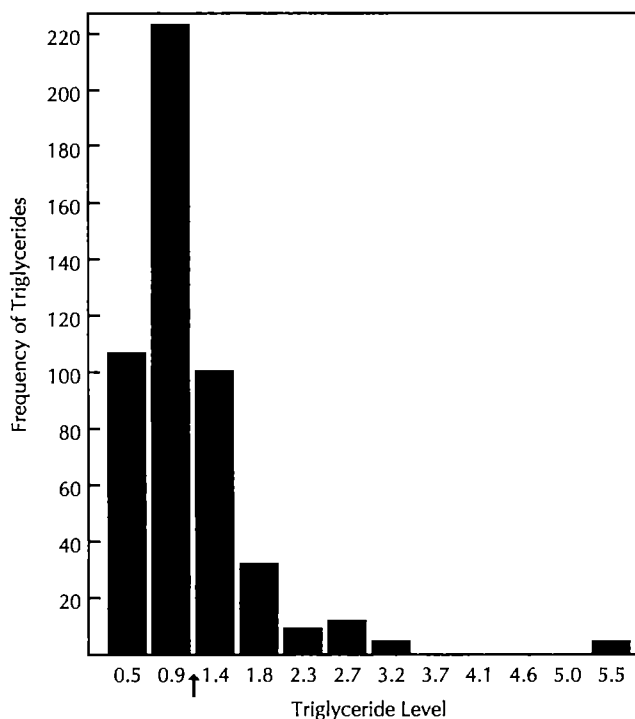


Fig 5.—Distribution of 500 patients according to triglyceride levels. Arrow indicates 95th percentile for age. All values are in micromoles per liter.

mg/dL) despite appropriate dietary changes, especially with a family history of premature coronary heart disease, were considered for referral.

An elevated HDL cholesterol level is antiatherogenic, and a low level is an independent risk factor for coronary artery disease.¹⁹ High-density lipoprotein cholesterol levels are not predictive of adult levels, however, until puberty, according to the Bogalusa Heart Study.²⁰ Fifty-three (10.6%) of the 500 patients studied were found to have HDL cholesterol levels above the 95th percentile of 1.8 mmol/L (70 mg/dL). Thirty-seven families could be contacted for questioning, and 11 (30%) reported a family member who had a myocardial infarction prior to 55 years of age. An abnormally low HDL cholesterol level of less

than 0.9 mmol/L (35 mg/dL) was observed in 20 children (4%), and seven of the 15 families contacted similarly reported a family member with premature myocardial infarction. The mean LDL cholesterol levels in these two groups of patients were 3.4 mmol/L (132 mg/dL) and 4.0 mmol/L (153 mg/dL), respectively, both well above the 95th percentile. High-density lipoprotein cholesterol levels in the studied population do not appear to be as important a predictor of coronary artery disease in their families as do LDL cholesterol levels. Children can have total cholesterol levels above the 95th percentile because their HDL cholesterol levels are very high. They are protected

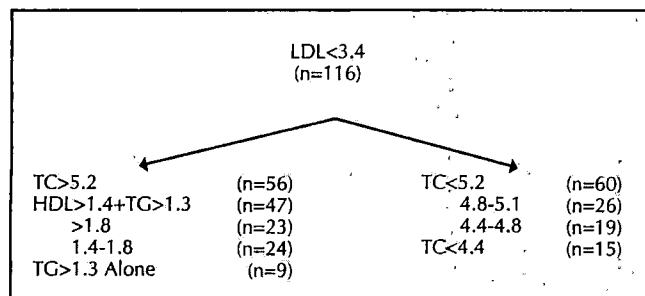


Fig 6.—Distribution of causative factors to explain why 116 originally hypercholesterolemic children had low-density lipoprotein (LDL) cholesterol levels below the 95th percentile on lipid profile testing. TC indicates total cholesterol; HDL, high-density lipoprotein; and TG, triglycerides. All values are in micromoles per liter.

and at reduced risk for future coronary artery disease. Only 5% (n=23) of the children who had lipoprotein profiles performed were originally identified as having hypercholesterolemia solely as a result of an elevated HDL cholesterol level.

Fifty percent of children found to have LDL cholesterol levels above the 95th percentile of 3.4 mmol/L (130 mg/dL) had no known family history of premature coronary heart disease or hypercholesterolemia. Of the 500 families of the children who had lipoprotein profiles performed, 374 could be reached for questioning and 123 (32%) reported having a family member who had a myocardial infarction prior to 55 years of age. The incidence of premature coronary heart disease in families of the children studied remained fairly constant regardless of the magnitude of their elevated LDL cholesterol levels. The Framingham Heart Study²¹ predicts an approximate 15% incidence of premature coronary heart disease in families of children who are not hypercholesterolemic.

The results of this study indicate that 85% of children identified with nonfasting total cholesterol levels higher than 5.2 mmol/L (200 mg/dL) by universal screening will have a definable phenotypic lipid disorder when a lipoprotein profile is performed. Thirty-two percent of such children can be expected to have a family member with a myocardial infarction prior to 55 years of age. Screening for elevated cholesterol levels leads to discussion of weight control, regular exercise, smoking avoidance, blood pressure monitoring, and reduction of dietary salt, cholesterol, and saturated fat. Advice and example regarding prudent life-style choices, early dietary intervention, and, in an appropriate few, pharmacotherapy surely will reduce the incidence of coronary heart disease in years to come.

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Outpatient Assessment of Infants With Bronchiolitis

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• Two hundred thirteen infants younger than 13 months with bronchiolitis were prospectively followed up to identify the historical, physical, and laboratory clues at initial emergency department evaluation that would help to predict disease severity. Based on their total course of illness, the patients were classified as having mild (139 patients) or severe (74 patients) disease, and the initial emergency department evaluation findings of these two groups were compared. Six independent clinical and laboratory findings were identified that were strongly associated with more severe illness: (1) "ill" or "toxic" general appearance; (2) oxygen saturation less than 95%, as determined by pulse oximetry; (3) gestational age, younger than 34 weeks; (4) respiratory rate, 70/min or greater; (5) atelectasis on a chest roentgenogram; and (6) age, younger than 3 months. The infant's oxygen saturation as determined by pulse oximetry was the single best objective predictor of more severe disease.

(AJDC. 1991;145:151-155)

Physicians are often faced with evaluating infants with bronchiolitis and deciding which infants have more severe disease that may require hospitalization. Respiratory syncytial virus (RSV) is probably the most important respiratory pathogen among young children and may cause serious morbidity and mortality.¹⁻⁶ Approximately 50% of infants will acquire RSV infection during the first epidemic that they experience, and approximately 13 infants per 1000 require hospitalization in lower income populations.⁶⁻⁹ Of particular concern is that hypoxemia is often present and may not correlate with the clinical impression of the severity of the disease.¹⁰ In addition, the risk factors for morbidity have been identified only among infants who have been already hospitalized and who represent the "tip of the iceberg" of this disease.^{7,10-21} The purpose of our study was to identify at the initial outpatient evaluation those historical, physical, and laboratory clues that may predict more severe disease.

Accepted for publication August 17, 1990.

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Presented in part at the Annual Meeting of the Ambulatory Pediatric Association, Washington, DC, May 3, 1988.

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PATIENTS AND METHODS

All children who presented to The Children's Hospital of Philadelphia (Pa) Emergency Department during the 1987 epidemic season for RSV bronchiolitis (January through April) and who were (1) younger than 13 months, (2) had signs of lower airway disease such as tachypnea, rales, or wheezing, and (3) had a history of a preceding upper respiratory tract infection were eligible for the study. Following routine emergency department evaluation and treatment by the resident physician and senior-level supervising physician, a disposition was made.

At this point, the infant's condition was reassessed by the emergency department attending staff who were present 24 hours per day, and study data were obtained. The severity of respiratory distress was assessed by using the Clinical Asthma score.²² General appearance was judged as "well appearing," "ill—not toxic," or "toxic" and also was quantified by using the Yale Observation Scale (YOS).²³ The infant's oxygen saturation in room air, both while the infant was quiet and while he or she was sucking on a bottle, was determined by using pulse oximetry. The oxygen saturation was read when the pulse oximeter (Nellcor Inc, Hayward, Calif) correctly reflected the infant's heart rate. Measurement of oxygen saturation was not part of the infant's routine evaluation.

Laboratory evaluation included anteroposterior and lateral chest roentgenograms that were subsequently read by a staff radiologist (N.H.S.) who was blinded to the clinical presentation of the patient. Nasopharyngeal aspirates were sent to the laboratory for viral isolation in tissue culture and for testing with a rapid immunoassay, RSV enzyme-linked immunosorbent assay^{24,25} (Abbott Laboratories, North Chicago, Ill), that detects the presence of RSV in respiratory secretions.

Infants enrolled in the study were scheduled for reevaluation by the primary investigators (K.N.S. and L.M.B.) 24 to 72 hours after the emergency department visit, and additional follow-up visits or telephone calls were made until the patient was judged to be clinically "well." After resolution of the symptoms, the enrolled infants were divided into "mild disease" or "severe disease" groups. Infants were judged to have had mild disease if they remained alert and active and were well hydrated while they were taking fluids orally throughout their illness. The initial emergency department evaluation findings of these two groups of infants were compared to establish which historical, physical examination, and laboratory clues were associated with severity of disease.

Only study information with an 80% or greater response or completion rate was included in the data analysis. The χ^2 , Mann-Whitney U, or *t* test was used to determine which individual components of the initial emergency department evaluation were associated with severity of disease, and the relative risk (RR) of having severe disease was calculated for each of these findings. Discriminant analysis was then used to determine a model of clinical and laboratory findings that would best predict illness severity. An a priori level of statistical significance was chosen at .05. The study protocol was approved by the hospital's Human Subjects Committee.

Table 1.—Historical Information Associated With Severity of Disease*

	% Total Disease Severe Disease Mild Disease (N=213) (n=74) (n=139)			RR	95% Confidence Intervals
History of cyanosis or apnea	5	12	1†	2.76	2.02-3.77
Gestational age, wk					
<34	5	27	13†	2.55	1.86-3.50
<37	25	43	15†	2.31	1.63-3.27
Age, <3 mo	24	38	16†	1.93	1.36-2.74
Decreased PO intake	65	77	58‡	1.82	1.15-2.90
Perinatal complications	41	54	34‡	1.70	1.18-2.46
URI symptoms, ≤3 d	48	58	43§	1.48	1.02-2.16

*RR indicates relative risk; PO, oral (by mouth); and URI, upper respiratory tract infection.

† $P<.001$.

‡ $P<.01$.

§ $P<.05$.

RESULTS

Study Population and Outcome

Of the 228 study infants with bronchiolitis who were evaluated in our emergency department, 213 had adequate follow-up to judge eventual outcome and severity of illness. Of the 148 patients (65%) who were initially discharged from the emergency department, 89 returned for follow-up appointments. The parents of an additional 44 patients were reached by telephone and were not requested to return because they reported improvement with normal oral feeding and activity. Ninety patients were admitted at some point during their illness (80 directly and 10 at follow-up visits).

Based on their total course of illness, the patients were classified into two groups: (1) 139 patients with mild disease (16 who were judged to be hospitalized inappropriately based on results of follow-up evaluations, and 123 who were discharged from the emergency department with resolution of their illness), and (2) 74 patients with more severe disease (64 who were hospitalized initially and 10 who were hospitalized at follow-up). Of these 74 patients with more severe disease, 59 (80%) received oxygen therapy, 13 (18%) were admitted to the intensive care unit, and eight (11%) underwent mechanical ventilation.

Historical Information

The average±SD age of the babies in the study was 5.6±3.1 months. Most of the patients were black (86%) and male (62%). This was a largely lower socioeconomic group, with 79% either having no medical insurance or receiving medical assistance.

Historical factors associated with more severe disease and their RRs are presented in Table 1. The sex of the infant, a history of exposure to a smoker in the family (66%), whether the baby had been breast-fed (14%), a history (37%) or family history (71%) of wheezing, and the parental report of the duration of wheezing (median, 4 days) were not associated with disease severity.

Table 2.—Physical Examination: Findings and Observations Associated With Severity of Disease*

	% Total Disease Severe Disease Mild Disease (N=213) (n=74) (n=139)			RR	95% Confidence Intervals
General appearance—"ill" or "toxic"	41	76	24†	4.56	2.71-7.69
Yale Observation Scale score, ≥10	24	52	12†	3.30	2.24-4.85
Accessory muscle use	46	72	33†	3.01	1.94-4.66
Clinical Asthma Score, ≥2	50	73	38†	2.68	1.71-4.21
Respiratory rate, per minute					
≥70	14	29	5†	2.60	1.90-3.57
≥60	37	54	28†	2.01	1.39-2.90
Rales	24	40	16†	2.09	1.44-3.02

*RR indicates relative risk.

† $P<.001$.

Physical Examination Findings

Most infants were described as "well appearing" on physical examination and were afebrile (68%, <38°C). Eighty-six percent had a YOS score less than 10 (scale, 6 through 30), and 50% scored less than 2 on the Clinical Asthma Score (scale, 0 through 10).

Physical examination findings associated with disease severity and their RRs are given in Table 2. The presence (86%) or degree of wheezing on auscultation, the infant's temperature, the presence of a cough (91%) or nasal discharges (82%), and subjective response to epinephrine hydrochloride.

Laboratory Evaluation

The RSV enzyme-linked immunosorbent assay test and viral-culturing techniques were able to identify a viral pathogen or chlamydia in approximately half of patients (48%). Respiratory syncytial virus constituted 42%, and parainfluenza (type III), enterovirus, and chlamydia constituted 2% each.

Infants with more severe disease had lower oxygen saturations as determined by pulse oximetry. Clinical judgment of a baby's color, which is used in the YOS, correlated with oxygen saturations below 95% in only 45% of the cases. Chest roentgenograms of the babies with more severe illness were more likely to show atelectasis and hyperaeration, but not peribronchial thickening. Respiratory syncytial virus was also subsequently identified more often in patients with more severe disease (Table 3).

Multiple-Factor Analysis

Discriminant analysis identified six clinical and laboratory findings that were independently and strongly associated with more severe disease: (1) general appearance of the infant, (2) oxygen saturation as determined by pulse oximetry, (3) gestational age, (4) respiratory rate, (5) presence of atelectasis on a chest roentgenogram, and (6) current age ($r=.67$, $R^2=.45$, $F=21.5$ [6, 158]). The combination of these six variables maintained good specificity

Table 3.—Laboratory Findings Associated With Severity of Illness*

	% Severe Disease (N = 213) (n = 74) Mild Disease (n = 139)			RR	95% Confidence Intervals
	Total	Disease	Disease		
Pulse oximetry—while quiet					
Oxygen saturation, <97%	25	54	11†	3.44	2.38-4.98
Oxygen saturation, <95%	12	32	2†	3.28	2.42-4.43
Pulse oximetry—while sucking					
Oxygen saturation, <97%	32	71	14†	5.19	2.71-9.97
Oxygen saturation, <95%	18	58	0†	6.31‡	3.83-10.39‡
Chest roentgenograms					
Atelectasis	9	21	2†	2.70	1.97-3.70
Hyperaeration	58	69	52§	1.58	1.03-2.42
Viral isolation					
RSV	42	52	35§	1.53	1.06-2.20

*RR indicates relative risk; RSV, respiratory syncytial virus.

† $P < .001$.

‡Estimated.

§ $P < .05$.

(91%) with higher sensitivity (76%) when compared with any individual factor (Table 4). The predictive values, positive and negative, were 81% and 88%, respectively. When only those infants with documented RSV infection were included, this group of findings was still good ($r = .68$, $R^2 = .46$, $F = 8.43$ [6, 59]) with a sensitivity and specificity of 86% and 91%, respectively, and predictive values (positive and negative, respectively) of 86% and 91%.

In an attempt to utilize only clinical observations during outpatient evaluation, as would occur in office practice, pulse oximetry and roentgenograms were removed from the regression equation and replaced with the "color" observation item on the YOS, which was strongly correlated ($r = .66$) with pulse oximetry results, but not as sensitive in discriminating low oxygen saturations. No individual clinical finding correlated well with atelectasis on a chest roentgenogram. This model ($r = .64$, $R^2 = .41$, $F = 23.7$ [5, 172]) was less sensitive in discerning severity of illness (65%), but maintained specificity (90%). Predictive values, positive and negative, were 74% and 85%, respectively.

Clinical Judgment at Initial Evaluation

Overall, clinical judgment, as reflected by the decision to admit babies to the hospital, was good in our emergency department, which has attending physician supervision at all times. However, too much importance may have been attributed to a history of prematurity in the presence of a benign evaluation, as the 16 infants who were hospitalized but had mild disease were more likely to have had a history of prematurity (42% vs 17%; $P < .04$). Otherwise, the initial

Table 4.—Model of Six Independent Factors Associated With Severity of Illness: Sensitivity, Specificity, and Predictive Value

	% Predictive Value			
	Sensitivity	Specificity	Positive	Negative
General appearance "ill" or "toxic"	76	76	60	87
Pulse oximetry—while quiet				
<97%	54	89	72	79
<95%	32	98	87	73
Gestational age, <34 wk	27	95	74	71
Respiratory rate, ≥ 70 /min	29	95	75	71
Chest roentgenogram with/without atelectasis	21	98	82	70
Age, <3 mo	38	83	55	72
Six-variable model	76	91	81	88

outpatient assessment of this group was indistinguishable from those infants with mild disease who were never hospitalized. A review of their hospital course found that none of these infants received oxygen, had apnea or bradycardia, or were observed for more than 48 hours.

The 10 babies who were initially thought to have mild disease at their initial emergency department assessment, but subsequently experienced more severe disease, were early in their course of illness as determined by the duration of their upper respiratory tract infection symptoms (3.8 vs 6.3 days; $P < .04$). They were also subsequently found to have RSV bronchiolitis as determined by enzyme-linked immunosorbent assay or culture (70% vs 34%; $P < .04$) compared with other infants who had mild illness and never required hospitalization.

COMMENT

This prospective study identifies several important components of the initial outpatient evaluation that can be used to assess severity of disease in babies with bronchiolitis. These results are contrary to findings of the retrospective study by McMillan et al,¹⁷ which stated that clinical parameters are ineffective in establishing the severity of disease in infants with bronchiolitis.

Our investigation suggests that the infant's gestational age at birth, more than the chronologic age, is the historical factor most strongly associated with illness severity. Although infants born prematurely may have a higher incidence of perinatal complications such as bronchopulmonary dysplasia and congenital lung or cardiac abnormalities, and, therefore, more severe bronchiolitis,^{7,16,17,20} gestational age at birth overshadowed the parental history of perinatal complications in predicting disease severity at initial outpatient assessment. Young postnatal age, although less important, also increased the infant's RR of having more severe bronchiolitis in our study and has been associated with increased risk of apnea,¹¹⁻¹³ hypoxemia,¹⁰ and respiratory failure^{14,17} among infants hospitalized for RSV. Other historical and

demographic factors that have been reported to increase the infant's likelihood of acquiring RSV or parainfluenza bronchiolitis, such as crowding or presence of older siblings,¹⁵ cigarette smoking in the household,^{7,15} a family history of allergies or asthma,^{7,15,18} a medical history of wheezing,¹⁸ male sex of the child,^{5,6} and lack of breastfeeding,^{18,21} were not associated with disease severity in our study.

On physical examination, the simple clinical description of the infant's general appearance ("well appearing," "ill—not toxic," or "toxic") by an attending physician was better at predicting illness severity in this group of patients than the Clinical Asthma Score,²² which was designed to evaluate persons with asthma, or the YOS,²³ which was initially designed to assess serious illness in febrile babies. Tachypnea, but not the presence or degree of wheezing, was also found to be a helpful measure in assessing the degree of illness. Although McMillan et al¹⁷ did not find that the degree of tachypnea at the time of hospital admission was associated with a prolonged hospital stay, the study was retrospective and included patients who had endotracheal tubes at the time of evaluation.

Lobar or streaky atelectasis on a chest roentgenogram was highly associated with more severe disease. Wildin et al²⁶ noted a significant correlation between lobar atelectasis and severity of illness in children hospitalized with RSV, parainfluenza, influenza, and adenovirus infections. In addition, Outwater and Crone¹⁴ noted that atelectasis or pneumonia was present on chest roentgenograms in all 15 of their study infants who had respiratory failure that required intubation. Although a chest roentgenogram may not be necessary in all outpatients with bronchiolitis, roentgenographic information can be a useful adjunct to clinical decision making and diagnosis.

We found the infant's oxygen saturation, as determined by pulse oximetry, to be the single best predictor of illness severity. Low oxygen saturation is often not clinically apparent. In one study, pulse oximetry that was done shortly after admission to the hospital on babies with RSV bronchiolitis found a mean oxygen saturation of 87%, with little correlation between clinical assessments of degree of hypoxia.¹⁰ Pulse oximeters give rapid, continuous, non-invasive, and valid measurements of oxygen saturation.²⁷⁻³⁰ Their rapid response time was able to detect changes in saturation that occurred when the infant was feeding.

A broad definition of mild and severe disease was used in classifying severity of illness in our study. Strict objective criteria (such as respiratory rate or pulse oximetry results) were not chosen to avoid preselecting for the parameters that we wished to evaluate at initial outpatient assessment. Without strict criteria, children with more moderate disease may have been included into either category. However, these infants would tend to bias the findings by making it more difficult (not less difficult) to distinguish differences between the two groups. Additionally, since severity of illness was based on eventual outcome during the course of illness, rather than a hospital admission decision, no infant who was initially discharged and experienced more severe disease was missed, and those infants with very mild disease who were admitted were identified.

We studied all infants with bronchiolitis and not just those with proved RSV infections, because at first evaluation, the viral cause is not often known. For this reason, and because no patients who bypassed the emergency department and were directly admitted were included, the severity of illness may have been lower than in other stud-

ies that have reported higher incidences of apnea¹¹⁻¹³ and longer lengths of hospitalization.^{10,16,17} However, the percentage of our hospitalized patients who required intensive care and mechanical ventilation was similar to that reported by other studies.^{7,10,16}

In summary, we were able to identify a group of six clinical and laboratory findings at initial outpatient evaluation that may aid in identifying infants with bronchiolitis who are at risk for having or experiencing more severe disease: (1) "ill or toxic" general appearance; (2) oxygen saturation less than 95% by pulse oximetry; (3) gestational age, younger than 34 weeks; (4) respiratory rate, 70/min or greater; (5) atelectasis on chest roentgenograms, and (6) postnatal age, younger than 3 months. We would highly recommend that emergency department evaluation of infants with bronchiolitis include pulse oximetry, as this simple and noninvasive test is the single best predictor of illness severity.

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Increased Transient Tachypnea of the Newborn in Infants of Asthmatic Mothers

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• **Objective:** To compare the incidence of transient tachypnea of the newborn (TTN) in infants of asthmatic vs nonasthmatic mothers.

Research Design: Case-control analysis.

Setting: Group model health maintenance organization.

Patients: A volunteer sample of 294 pregnant asthmatic women and 294 pregnant nonasthmatic women with normal pulmonary function test results, matched on the basis of age and smoking status. All subjects entered the study before their third trimester of pregnancy. Subjects with multiple gestations and abortions (<20 weeks' gestation) were excluded.

Intervention: Asthma was treated in the allergy department. Routine obstetric, neonatal, and pediatric care was provided to all patients by staff physicians.

Measurements/Results: Transient tachypnea occurred in 11 infants (3.7%) of asthmatic women and in one control infant (0.3%). There were no significant differences between asthmatic and matched control subjects in previously defined TTN risk factors, such as the occurrence of longer labors, failure to progress, cesarean sections, premature births, male sex, Apgar scores of less than 7 at 1 minute, or birth weight greater than 4 kg. Although infants of asthmatic mothers were more likely to exhibit wheezing by age 15 months compared with control infants (12.0% vs 3.2%), none of the infants with TTN manifested wheezing by age 15 months. No relationships could be identified in the asthmatic cohort between the occurrence of TTN and asthma severity or medication use (during the pregnancy in general or during labor and delivery in particular).

Conclusion: Although the mechanism is uncertain, maternal asthma appears to increase the risk of infant TTN.

(AJDC. 1991;145:156-158)

Transient tachypnea of the newborn (TTN) was first described in 1966¹ and is a common cause of respiratory distress in the newborn.² It is typically associated with radiologic characteristics of so-called wet lung disease,³

but its exact etiology and pathogenesis remain obscure. Although TTN is usually benign and self-limited,¹ recent reports emphasize that affected infants may experience substantial morbidity,⁴⁻⁷ including profound hypoxemia, and may need mechanical ventilation. In an attempt to further understand this condition, recent studies have attempted to identify maternal, obstetric, and neonatal characteristics associated with TTN.^{7,8} We suggest that maternal asthma should be added to the list of conditions that increase the risk of TTN.

SUBJECTS AND METHODS

Subjects

Subjects for this study were participants in the Kaiser-Permanente Prospective Study of Asthma During Pregnancy, conducted at Kaiser-Permanente Medical Center, San Diego, Calif, the design of which has been previously described.^{9,10} Briefly, all asthmatic patients registering for prenatal care before their third trimester were recruited and matched with nonasthmatic (control) subjects according to age and smoking status. Asthma was defined as a history of chest wheezing, chest tightness, or chest cough that could be precipitated by infection, exercise, and/or allergens and could be relieved either spontaneously or by bronchodilator medication. The medical history was substantiated by demonstration of reversible airway obstruction (as previously defined¹⁰) on pulmonary function tests or by documentation of auscultatory wheezing during tidal breathing. All subjects completed pulmonary function tests at 7 months' gestation and/or after birth. Control subjects with abnormal pulmonary function test results were excluded from the study. The study was approved by the Kaiser-Permanente Institutional Review Board, and informed consent was obtained from all subjects.

Asthma was treated by an allergist (M.S.) who attempted to prevent acute asthmatic episodes and asthma symptoms that interfered with sleep or normal activity. Data were evaluated from singleton pregnancies ending in birth between June 1978 and December 1984. Subjects undergoing abortions (<20 weeks' gestation) were excluded. Asthmatic patients (n = 66) for whom suitable controls were not available were not included in the analysis. The final cohort included 294 asthmatic subjects and 294 matched controls. Fifteen-month follow-up data were available for 217 infants of asthmatic mothers and for 218 control infants.

Measurement of Variables

Perinatal outcome data were extracted from the standard obstetric and nursery medical records and 15-month infant data were taken from the pediatric medical records by a research nurse (K.M.H.) who did not know at the time of data collection to which group (asthma vs control) the subject belonged. The diagnosis of TTN was made by the attending neonatologist based on the

Accepted for publication September 4, 1990.

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A Comparison of the Prevalences of Transient Tachypnea of the Newborn (TTN) and Other Relevant Perinatal Variables in the Pregnancies/Infants of Asthmatic Patients vs Matched Control Subjects

Parameter	Incidence, %	
	Asthmatic Group (N=294)	Control Group (N=294)
TTN	3.7	0.3
Maternal age >35 y	2.0	2.0
Maternal smoking	5.4	5.4
Multiparas	58.5†	34.4
Longer labor	50.9	49.1
Failure to progress	1.4	2.0
Cesarean section	20.1	19.0
Premature birth (<37 weeks' gestation)	5.8	3.4
Male sex	50.7	54.1
Apgar score <7 at 1 min	9.4	8.7
Birth weight >4 kg	8.5	12.9
Infant respiratory distress syndrome	1.0	0.7

* $P = .003$. Remains significant at the 5% level when the type 1 error is adjusted for multiple comparisons using Bonferroni's significance level.

† $P < .001$. Remains significant at the 5% level when the type 1 error is adjusted for multiple comparisons using Bonferroni's significance level.

following criteria: (1) onset of tachypnea (respiratory rate >60 breaths per minute) within 6 hours after birth; (2) persistence of tachypnea for at least 12 hours; (3) chest roentgenographic abnormalities consistent with TTN (ie, mild cardiomegaly, increased perihilar markings, perivascular cuffing, fluid in the lung fissures, and hyperinflation); and (4) exclusion of infant respiratory distress syndrome, meconium aspiration, air leak, congenital pulmonary abnormalities, and significant congenital heart disease. A wheezing episode in the first 15 months of life was defined as wheezing on chest auscultation documented in the pediatric records on at least one occasion.

The following perinatal variables were also evaluated: maternal age greater than 35 years (at entry to study), maternal smoking (>10 cigarettes per day for at least 1 month of pregnancy), parity (primipara vs multipara), labor longer than the median from this series (excluding births by cesarean section, with the median for primiparas and multiparas calculated separately), failure to progress, cesarean section, premature birth (<37 weeks' gestation), male sex, Apgar score of less than 7 at 1 minute, birth weight greater than 4 kg, and infant respiratory distress syndrome. In addition, the following asthma severity and gestational medication variables were assessed: overall severity (medication requirements), emergency treatment requirements, mean gestational forced expiratory volume in 1 second, and medication use any time during the pregnancy or specifically during labor and delivery (eg, inhaled bronchodilators, theophylline, or corticosteroids).

Statistical Methods

For all analyses, two-tailed statistical significance was set at the 5% level. In the case-control analyses, the prevalences of the perinatal variables were compared between asthmatic patients and matched controls by χ^2 analysis when the minimum expected value was greater than or equal to 5 and by Fisher's Exact Test otherwise.

In the asthmatic cohort, the relationship of the occurrence of TTN to the maternal asthma severity and medication variables described above were evaluated by χ^2 analysis for linear trend.¹¹ This type of analysis identifies linear relationships between an

increasing prevalence of TTN and an increasing intensity of the asthma severity and medication variables. The relationship of the occurrence of TTN to maternal asthma medication use during labor and delivery was evaluated in the asthmatic cohort by Fisher's Exact Test.

RESULTS

The prevalences of TTN and other potentially relevant perinatal variables in asthmatic vs matched control subjects are shown in the Table 1. Transient tachypnea of the newborn occurred in 11 (3.7%) of 217 asthmatic subjects, but in only one (0.3%) of 294 control infants ($P = .003$). Multiparity was also significantly more common in asthmatic vs control subjects. However, when primiparas and multiparas were considered separately, the prevalence of TTN in the infants of asthmatic primiparas (5.0%) was significantly greater ($P = .003$) than the prevalence in control primiparas (no instances of TTN), and the prevalence in asthmatic multiparas (2.9%) was higher than that in control multiparas (1.0%), although this difference did not reach statistical significance.

Two of the infants with TTN were premature. However, the lung profile of one of them (lecithin-sphingomyelin ratio >5, phosphatidylglycerol present) was not consistent with surfactant deficient respiratory distress syndrome. Although a lung profile of the second infant was not available, the clinical course and oxygen requirements were consistent with TTN rather than infant respiratory distress syndrome.

Infants of asthmatic mothers were much more likely to experience a wheezing episode by age 15 months (12.0%) than were infants of control mothers (3.2%) ($P < .001$). However, none of the infants with TTN manifested wheezing by age 15 months. There were no significant relationships between any of the asthma severity or medication variables and the occurrence of TTN in asthmatic mothers (data not shown).

COMMENT

The Kaiser-Permanente Prospective Study of Asthma During Pregnancy was designed to evaluate obstetric and infant outcomes in prospectively treated asthmatic subjects compared with matched, simultaneously followed nonasthmatic controls. Although there was no significant increase in the occurrence of respiratory distress syndrome in the infants of asthmatic vs control subjects, a significant increase in the incidence of TTN was observed in infants of asthmatic mothers (Table). Although four prior studies have compared outcomes in the infants of asthmatic vs control mothers,¹²⁻¹⁵ none of these reports mentioned TTN.

Since the exact etiology of TTN is unclear and because TTN can be a cause of substantial neonatal morbidity,⁴⁻⁷ recent studies have attempted to identify maternal, obstetric, and neonatal characteristics that may be associated with TTN. Gross et al⁷ compared 55 pregnancies in which the neonate developed TTN with 355 pregnancies in which infant respiratory distress did not occur. Of 14 parameters evaluated, negative amniotic fluid phosphatidylglycerol levels, premature delivery, and an Apgar score of less than 7 at 1 minute each made an independent contribution to the overall characterization of infants at risk for TTN. Rawlings and Smith⁸ compared clinical data from 100 neonates with TTN with data from 100 healthy neonates. The prevalence of male sex and macrosomia were significantly higher in the infants with TTN, and the obstetric histories of mothers of infants with TTN were characterized by longer labor, a higher prevalence of failure to progress in labor, and a higher proportion of cesarean sections.

The increased occurrence of TTN in infants of asthmatic mothers that was observed in this study could not be explained by differences in the occurrence of previously defined risk factors between the asthmatic and control groups (Table). Although the asthmatic and control groups were not well matched for parity, parity has not been previously defined as a risk factor for TTN, and the incidence of TTN remained higher in infants of asthmatic vs control subjects when primiparas and multiparas were evaluated separately.

The occurrence of TTN in infants of asthmatic mothers was not related to maternal asthma severity, degree of control (ie, occurrence of acute episodes and gestational pulmonary function), or medication use (during the pregnancy in general or during labor and delivery in particular). However, the relatively small number of infants manifesting TTN makes the power of this analysis small.

Although infants of asthmatic mothers were significantly more likely to wheeze during the first 15 months of life than were infants of nonasthmatic mothers, the occurrence of TTN in infants of asthmatic mothers was not associated with subsequent wheezing within this period. This, of course, does not preclude an increased risk of asthma developing later in infants with TTN. Indeed, a recent study of 58 children evaluated at ages 4 to 5 years who demonstrated TTN at birth revealed significantly more clinical findings consistent with asthma than in 58 controls who did not demonstrate TTN at birth.¹⁶

One potential mechanism for both increased instances of TTN and subsequent asthma in infants of asthmatic mothers would be a genetic predisposition to β -adrenergic hyporesponsiveness, since animal studies suggest that the β -adrenergic system is important in the increased pulmonary fluid absorption and decreased production that normally occurs after birth,¹⁷ and β -adrenergic hyporesponsiveness¹⁸ associated with a reduction in the number of β -adrenergic receptors¹⁹ may be important in the pathogenesis of asthma. Further studies are necessary to establish the mechanisms of the relationships between maternal asthma, infant TTN, and childhood asthma. However, our current results suggest that maternal asthma is an independent risk factor for the development of infant TTN.

This is the fourth report from the Kaiser-Permanente Prospective Study of Asthma During Pregnancy. The study was supported in part by grant AI20426 from the Allergy and Asthma Branch of the National Institute of Allergy and Infectious Diseases, Bethesda, Md, and by grants from William H. Rorer—Dooner Laboratories, Ft Washington, Pa, and Kaiser Foundation Hospitals, San Diego, Calif.

We thank Linda M. Chilingar for performing the statistical analysis, and Richard P. Porreco, MD, and Abram S. Benenson, MD, for reviewing the manuscript. We also thank Tamara Haydon and Patricia Stanwood for typing the manuscript and the staff from the Kaiser Foundation Hospital Medical Library for their assistance with the references.

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Correction

Errors in Table

In the article by Avner et al entitled "Acquired Methemoglobinemia," published in the November 1990 issue of *AJDC* (1990;144:1229-1230), there were errors in the Table. On page 1230 in the Table, in the entries under the column headed "Methemoglobin," no decimal points should appear.

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Please see brief summary of Prescribing Information on the next page.

References:

1. Watson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther.* 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

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CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

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Patients on PediaProfen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

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The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

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A Medical Ethics Issues Survey of Residents in Five Pediatric Training Programs

Bruce David White, DO, JD; Gerald B. Hickson, MD; Rosemary Theriot, EdD; Richard M. Zaner, PhD

• Few pediatric training programs offer formal instruction or have ethics consultants to assist residents with ethical dilemmas. Moreover, even if such assistance were available, it is not clear that educators have an adequate understanding of (1) the range and frequency of possible ethical dilemmas residents may encounter, (2) residents' most troublesome concerns, (3) their use of resources to resolve issues, and (4) their own ethics belief systems. A sample of convenience (51 residents) at five midsouth residency programs was queried during 25-minute open-ended interviews to answer ethical questions; there were no refusals to participate. The "most troublesome" cases cited by the residents were related to life-and-death issues (withholding and withdrawing life support), child abuse and neglect cases, and disputes regarding patient care that arise between services. Two thirds of those surveyed indicated that they are still somewhat troubled by these difficult ethical problems. Surprisingly, residents stated that they relied on their peers more often than their attending physicians for effective assistance in resolving their most troublesome dilemmas. We support continuing education and research efforts to help residents and educators feel "more comfortable" in resolving ethical dilemmas.

(AJDC. 1991;145:161-164)

Residents and residency educators should seek to identify and evaluate the moral problems and ethical dilemmas that they expect to encounter in the practice of medicine for two practical reasons. First, residency training represents a highly stressful time for young physicians.^{1,2} A principal stressor is the recognition that one becomes personally responsible for the care and well-being of patients. Many believe that "caring for patients" means more than attending to a patient's immediate physical needs. Anxieties may arise within any physician confronted by the moral problems with which patients may present. Simultaneous attempts to treat physical maladies

and resolve ethical dilemmas can prove to be especially overwhelming to those with little training in clinical medicine or ethics.³ Second, the increase in medical litigation may be due to physicians' failure to communicate thoroughly and adequately with their patients.⁴ This communication problem is particularly troublesome, perhaps approaching one of avoidance, when physicians are uncomfortable in dealing with the ethical dilemmas that arise during the course of patient care.⁵

Residency program directors attempt to prepare physicians-in-training for the medical problems that they may encounter in practice, yet few programs incorporate patterned instruction for the resolution of ethical dilemmas (C. Strong, J. E. Connelly, unpublished data, 1989). There may be several reasons for this posture. Some attending physicians believe that they lack the necessary training to adequately discuss ethical issues, maintain that certain ethical problems cannot be solved or that methods of resolution cannot be instilled, or sense that it takes too long (on rounds or in a busy clinic) to properly address such issues. Some attending physicians believe that "ethics cannot be taught" in the limited time available for residency education.⁶ Whatever the reasons, residents often complete their training without satisfactory medical ethics instruction during the course of their graduate medical education.

This may be changing. Several medical ethicists have suggested a range of topics and goals for undergraduate medical ethics education, including "the ability to identify the moral aspects of medical practice," "the ability to obtain a valid consent or a valid refusal of treatment," "the ability to decide when it is morally justified to withhold

Department Editors.—Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—How do we train our residents in issues dealing with ethical decisions? Whom do they rely on for advice? White et al offer some interesting insights into these issues and offer suggestions for our training programs. Maybe ethics can be taught. —H.D.A.

Accepted for publication May 1, 1990.

From The Center for Clinical and Research Ethics, Vanderbilt University Medical Center (Drs White, Hickson, and Zaner), and The Clinical Research Center, Meharry Medical College (Dr White and Ms Theriot), Nashville, Tenn.

Read before the annual meeting of the Residency Interest Group of the Society for Health and Human Values, Washington, DC, October 27, 1989.

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information from patients," and "a knowledge of the moral aspects of the care of patients with a poor prognosis [including patients who are terminally ill]."⁷ Others have proposed remedies that involve the introduction of ethics training through lectures, discussions, conferences, and courses⁸ in pediatrics,⁹ neonatology,¹⁰ perinatology,¹¹ and obstetrics.¹² Recently, some medical centers have established medical ethics consult services to provide ethics instruction on a case-by-case basis within the acknowledged context of direct consultative patient care.¹³

In light of previous deficiencies and an increasing interest in medical ethics education, it was believed that a descriptive study should precede any curricula recommendations for our own institutions. We therefore conducted a survey to identify (1) the moral problems or ethical dilemmas that pediatric residents had confronted in their episodic training experiences, (2) each resident's single most troublesome ethical challenge, (3) the resources they had used to assist them in coping with these dilemmas, and (4) whether these issues were resolved. Perhaps a medical ethics instruction program focused on residents' experiences and needs will be better accepted by pediatric educators and physicians-in-training.¹⁵

MATERIALS AND METHODS

An open-ended questionnaire was developed specifically to gather the information described above and included questions to ascertain residents' sociodemographic characteristics. The instrument was reviewed by philosophers and pediatric educators and was compared with similar survey questionnaires.¹⁵

Continuity-care clinic directors and chief residents at five mid-south pediatric training sites were contacted about the possibility of administering the survey at their institutions. All five of the following centers agreed to participate: Hubbard Hospital of Meharry Medical College, Nashville, Tenn; Kosair Children's Hospital (a teaching hospital of the University of Louisville [Ky]); LeBonheur Children's Medical Center (a teaching hospital of the University of Tennessee [Memphis]); Metropolitan Nashville General Hospital; and Vanderbilt Children's Hospital, Nashville. One of us (B.D.W.) visited the five sites and administered the questionnaires to all participants. The sample of convenience included pediatric and combined medicine-pediatric program residents who held their continuity-care clinics on either Wednesdays or Thursdays at the various sites. Each resident was informed about the purpose of the study, was asked to participate, and gave oral consent. Fifty-two residents agreed to participate; none refused. One resident was called away before the interview was completed.

Resident responses were recorded by the interviewer and were repeated to each resident to ensure recording accuracy. Interviews averaged 25 minutes each. We categorized the responses to the open-ended questions to aid in conceptualization and data analysis. Consistency in categorization was verified by two consultants (a philosopher and a nurse clinician).

RESULTS

To identify the single greatest moral and ethical dilemma that each resident had faced and to document the wide range of moral and ethical problems that they might encounter in the future, a series of questions were posed. In answer to the question "What ethical dilemmas have you confronted in practice?" the 51 residents offered 109 total responses, or 2.14 responses each. The majority involved the life-and-death issues of withdrawing care (57%) or withholding life support (9%). Other responses included dealing with teenage pregnancies, birth control, and abortions (16%); facing the economic, legal, and social conflicts that arise in medical practice (9%); genetic counseling (4%); managing personal and societal uncertainties when reporting abuse and neglect (4%); and balancing professional responsibilities with family life (1%).

Table 1.—Respondents' Most Frequently Cited Troublesome Cases*

Category 1: Life and Death Issues (88%)

"Terminating care" or electing to discontinue "extraordinary care" in severely ill patients with an expected poor prognosis (24/47 [47%])

Withdrawing support from a patient in the neonatal intensive care unit (10/47 [20%])

Withholding life support in the extremely premature neonate (gestational age, ≤ 26 weeks) (often with or expected intracranial hemorrhage) in the delivery room (7/47 [21%])

Category 2: Abuse Cases (8%)

Reporting a physical or sexual abuse case encountered in the outpatient clinic or emergency department (4/47 [8%])

Category 3: Service Conflicts Cases (4%)

"Mediating between various services" with different opinions regarding treatment (2/47 [4%])

*Forty-seven (92%) of 51 residents responded.

Respondents were asked to review their lists and to identify the one case that had presented their single "most troublesome" ethical dilemma; 47 residents (92%) complied. In Table 1, the residents' most troublesome cases are divided into three categories. The vast majority of these cases (88%) involved life-and-death issues. There were, however, three subgroups with clearly distinguishing features. The two largest of these (67%) involved residents' concerns about withdrawing care (most often related to the process of actually removing life support, meaning extubation of a terminally ill patient with imminent cessation of all bodily functions) in either a neonate or an older child. The other subgroup (21%) included cases in which the resident had to decide, often within the confines of a delivery room, whether an extremely premature infant was actually viable and if, in retrospect, he or she had made the "right" decision. This subgroup also included the decisions that had to be made when faced with the birth of a seriously handicapped newborn, such as a child with trisomy 13 or 18. The second category (8%) involved questionable physical and sexual abuse cases, with residents asking how certain anyone could be that documented injuries actually occurred as a result of abuse. The remaining cases (4%) concerned professional conflicts that occurred when two services disagreed in their concurrent care for a terminally ill child.

Residents were then asked the following question: "Why do these issues become moral problems or ethical dilemmas?" The responses (110 total responses, or 2.16 per resident) included the following: these issues deal with the essence of medical practice in the physical care for the ill and show that decision making in treating patients cannot be separated from resolving ethical dilemmas (28%); these issues mark the tolerance one must accept with the uncertainties inherent in medical practice (18%); these issues prove the necessity to balance patient and societal as well as personal interests in medical practice that may conflict (17%); these issues illustrate the application of fundamental ethical principles, such as honesty, goodness, and justice (16%); these issues document that a number of external factors beyond the physician's control influence medical practice considerations (12%); these issues show that personal and staff conflicts may arise in medical practice (6%); and these issues demonstrate a lack of training in dealing with moral problems or ethical dilemmas (3%).

Respondents were also asked whether the most troublesome case identified was now "completely settled" in their own minds or if there were aspects of the case that were still of occasional concern. Thirty-six residents (71%)

Table 2.—Reasons 36 Respondents Gave as to Why Their Most Important Ethical Dilemma Was Not Resolved

Physician-Oriented

The dilemma recurs; it is a widely prevalent problem; each case must be individualized.

"I wonder if what we did was appropriate; was right."

"I have trouble talking to parents in these cases."

"The physician is helpless to effect any change."

It is painful for caregivers to see the consequences of treatment. There are legal consequences to what we did.

Patient and Family-Oriented

"We caused pain and discomfort" and did not appear to affect the ultimate outcome.

"What quality of life have we obtained; did we do any good?"

"We created false hopes."

"Parents did not take an active role [in decision making]."

"The mother and siblings are innocent victims [now too]."

"I feel sorry for the parents and family who live with the consequences."

The decisions are made in an emotional, stressful climate.

Disease-Oriented

"The prognosis was hopeless."

"The prognosis is still uncertain in these cases."

indicated that their most troublesome case was not resolved for the reasons given in Table 2. Nine (18%) indicated that their most troublesome case was now resolved. Examples of their reasons included the following: "we did all that could be done"; "we did the right thing"; "I've accepted the consequences"; and "the child survived." Six respondents (12%) did not answer this question.

In an attempt to assess how residents strive to deal with these issues, each respondent was asked if assistance had been sought from other individuals or services to resolve this most troublesome case. If assistance was requested, the residents were asked to list the relationship of the individual or the service to the case and then to rate the overall perceived effectiveness of that assistance on a five-point Likert scale (with 1 indicating "detrimental," 5 indicating "beneficial," and 3 being "neutral"). Forty-one residents (79%) indicated that they sought assistance from 106 sources (2.6 sources per resident). Some of the more frequently cited individuals and services are shown in Table 3, with the total number of times assistance was sought along with mean ratings. Attending physicians participated in 83% of these cases with a mean rating of 3.74, and peers participated in 51% of the cases with a mean rating of 4.14.

RESPONDENTS' CHARACTERISTICS

The 51 responding residents represented 29% of the total house staff serving in the participating residency programs. Most (n = 41) had graduated from medical school after 1985. They were almost equally divided among first-year (n = 17), second-year (n = 12), and third-year (n = 20) residents. One was a fourth-year medicine-pediatrics resident, and one respondent did not indicate level of training. About half were male (n = 26), and most were white (n = 37), married (n = 29), and without children (n = 38). Sixty-one percent (n = 30) were Protestant, 14% (n = 7) were Catholic, 12% (n = 6) were Jewish, and 14% (n = 7) indicated another or no religious preference. Eighty-two percent indicated that religion was either "important" or "very important" in their lives. Sixty-seven percent (n = 34) indicated that they had previously taken a course in "medical ethics." Thirty-seven percent (n = 19) said that

Table 3.—Effectiveness of Those Whom 41 Respondents Asked for Assistance*

	No. of Times Listed	No. Listed as "Beneficial" (Rating >3)	Mean Rating
Physicians			
Attending physician	34	24	3.74
Supervising resident and peers†	21	18	4.14
Supporting staff			
Nursing staff and social services staff†	12	9	4.16
Patient and family			
Patient and patient's parents and family†	4	4	4.75
Others			
Resident's spouse/significant other†	12	10	4.08

*Responses were rated on a scale of 1 (detrimental) to 5 (beneficial).

†Combined categories.

Table 4.—Sources of Respondents' Ethics Belief System*

Source	Rating
Family	4.55
Personal study and reflection	4.52
Religious teachings	4.20
Clinical experience	3.82
Some decisive personal experiences	3.82
Teachers	3.80
Personal understanding of societal needs	3.63
Peers	3.40
Societal contacts	3.10

*Responses were rated on a scale of 1 (added nothing) to 5 (added greatly).

they had been on at least one service team that had requested a "medical ethics consult" concerning one of their assigned patients.

Participants were asked to rate the degree to which a number of identified sources (for example, "family," "teachers," or "religious teachings") had contributed to their individual belief systems. The mean ratings are shown in Table 4.

COMMENT

Patterned educational efforts in medical ethics instruction might be better received if proportionately channeled into already identified problematic areas. An obvious purpose of our study is to illustrate the importance that residents attach to these issues (as shown by the insightfulness of their responses) and to serve as a marker for topic and resource allocation. For example, discussions of the withdrawal of life support (mentioned as a possible dilemma by more than half of the respondents) would appear to be a principal focus for life-and-death discussions. Ethics topics, however, like other points in most medical subject areas, should be selected for other reasons as well. Instructors would be ill-advised to teach and discuss *only* the problems that residents identified from their still rather limited practice perspective to the exclusion of other issues

that are widely recognized because of history, principle, and anticipated future effect.

Residents stated that they turned to attending physicians for assistance and support in resolving the ethical dilemmas presented by their most troublesome cases (83% [34/41]). They also sought assistance from supervising residents (17% [7/41]), peers (34% [14/41]), and fellows (5% [2/41]), but to a lesser degree than attending physicians. It seems curious then that the rating for attending physicians (3.74) was low compared with that for supervising residents (4.14), peers (4.14), and fellows (4.00); in fact, some might have expected the reverse given the fact that residents stated that teachers contributed to their belief systems to a higher degree (3.80) than did peers (3.40). Some might wonder whether this is so because the attending physician is a little more "distant" from the patient's bedside than are the residents. (This may be supported by the fact that the residents rated patients [4.50 mean rating from two responses] and families [5.00 mean rating from two responses] higher than any other source in assisting in the resolution of those most troublesome cases. Residents' spouses, however, scored higher than attending physicians as well [4.09 mean rating from 12 responses]. Perhaps the important factor here is whether the attending physician is "distant" from the residents' perception or discussion of the case.) In the defense of the attending physician, one should recall that ultimate legal (and moral) responsibility of patient care does not lie with the residents. Residents may often lack the "big picture" of overall patient care because of their limited hospital involvement and have varied expectations of their attending physicians' abilities and responsibilities. Efforts directed to increase attending physician "effectiveness"—or better yet to eliminate their "detrimental assistance"—and to increase peer involvement might enhance the resolution of moral problems in practice (or at least the residents' understanding of resolution).

Residents indicated that "clinical experience" (rated 3.82), "decisive personal experiences" (rated 3.82), and "teachers" (rated 3.30) contribute to their ethics systems. These answers show that residents' systems can at least be influenced in these areas by theoretical and practical education.

Our survey was somewhat limited for the purposes expressed herein. As with almost any survey, one may question the motives and appropriateness of the respondents' answers and the editorial control exercised by the authors in the formulation of outlines and answer categorizations. The size of the sample population is relatively small (approximately 180 total residents in the programs selected), about one third of whom were interviewed. Even with the open-ended questions, there may be a failure to reflect the "real world" of medicine in the instrument—accentuating the economic, legal, and social aspects of health care—in any ethical decision-making discussions. This may suggest that the survey should be administered in other areas of the country and among different specialty groups.¹⁶

A CLOSING SUGGESTION

Our results document the unique perspective of a representative sample of pediatric residents to a number of propounded open-ended questions about ethics issues. Some may feel that those results raise more questions than

they actually answer. Our study definitely identifies the need for further investigation in this area. However, this inquiry demonstrates that perhaps "ethics can be taught" or at least influenced. Residents indicated that teachers contribute greatly to their ethics belief systems and residents also evidenced their willingness to turn to attending physicians and peers in search of "solutions" to moral problems in medicine. With greater educational efforts and attempts on the part of staff, physicians-in-training would perhaps learn to feel "more comfortable" and more at ease in resolving ethical dilemmas as they do "more routine" medical practice concerns.

This work was supported in part by grant RR08198 from the GCRC and MBRS Branches of the Division of Research Resources, National Institutes of Health, Bethesda, Md.

The encouragement of Mary Ann South, MD, Director of the Clinical Research Center at Meharry Medical College, and the assistance of the continuity care clinic directors and the chief residents of the participating training programs are gratefully acknowledged. The editorial assistance of Martin E. Hamner, PhD, is deeply appreciated.

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WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, OTHER BLOOD DYSCRASIAS AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT.

SEPTRA SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions. Cough, shortness of breath, and/or pulmonary infiltrates may be indicators of pulmonary hypersensitivity to sulfonamides. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Complete blood counts should be done frequently in patients receiving sulfonamides.

SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies have documented that patients with group A β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin, as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

PRECAUTIONS:

General: Septra should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

Use in the Elderly: There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, or generalized bone marrow suppression or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function.

Use in the Treatment of *Pneumocystis carinii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): The incidence of side effects, particularly rash, fever, leukopenia, and elevated aminotransferase (transaminase) values with Septra therapy in AIDS patients who are being treated for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of Septra in non-AIDS patients.

Information for Patients: See full product information.

Laboratory Tests: Complete blood counts should be done frequently in patients receiving Septra; if a significant reduction in the count of any formed blood element is noted, Septra should be discontinued. Urinalysis with careful

microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that Septra may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Septra is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Septra may inhibit the hepatic metabolism of phenytoin. Septra, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: Septra, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with Septra.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1000 times human plasma levels in these same cells a low level of chromosomal damage was induced at one of the laboratories.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy: (See CONTRAINDICATIONS) Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim. In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

Nursing Mothers: See CONTRAINDICATIONS.

Pediatric Use: See CONTRAINDICATIONS.

ADVERSE REACTIONS: The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). (See WARNINGS section.) For more information on adverse reactions, see full product information.

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Intraosseous Infusion of Dobutamine and Isoproterenol

John F. Bilello, MD; Kevin C. O'Hair, DVM; William C. Kirby, MD; John W. Moore, MD

● Intraosseous infusion has been advocated as an emergency route in sick infants and children when intravenous access is not readily obtainable. Dobutamine hydrochloride and isoproterenol hydrochloride are useful emergency drugs that have not been studied when administered into the bone marrow. In a swine model, we compared the physiologic responses (heart rate, arterial pressure, and cardiac output) of dobutamine and isoproterenol infusions delivered intravenously and intraosseously during 20-minute intervals. We observed statistically significant effects of both dobutamine and isoproterenol delivered by the intraosseous route. In addition, the effects resulting from intraosseous infusion were statistically similar to those resulting from intravenous administration of these drugs. We conclude that the intraosseous infusion of dobutamine and isoproterenol is an effective and useful method for emergency administration of these medications.

(AJDC. 1991;145:165-167)

Delayed intravascular access has been recognized as a substantial obstacle to the successful resuscitation of pediatric patients in impending or frank cardiopulmonary arrest or shock. A recent study from a pediatric emergency department showed that it took more than 10 minutes to obtain venous access in 24% of cases of cardiac arrest. Intravenous access was never achieved in 6% of cases.¹

Therapeutic intraosseous infusion was described in 1934 for injection of a liver preparation in the treatment of pernicious anemia.² Tocantins et al^{3,4} described rapid absorption of various substances into the systemic circulation via the bone marrow. Several authors subsequently published reports of successful intraosseous infusions with few complications.⁵⁻¹² In 1977, Valdes¹³ published his personal experience with emergency fluid administration via the bone marrow. Intraosseous infusion has continually been supported as an appropriate means of intravascular access in emergency situations.¹⁴⁻¹⁶ Berg¹⁷ published a case re-

port of continuous infusion of dopamine and dobutamine in a pediatric patient, and Hodge¹⁸ reviewed the methods and complications of pediatric intraosseous infusions.

Controlled studies of intraosseous infusions in animal models have supported the efficacy and potential benefit of emergency medications infused through the bone marrow when intravenous access is not available.¹⁹⁻²² To our knowledge, no controlled study of the intraosseous infusion of either dobutamine or isoproterenol has been reported. The purpose of this study was to determine whether the intraosseous delivery of these drugs is as effective as the intravenous administration.

MATERIALS AND METHODS

The experimental protocol was reviewed and approved by the Department of Clinical Investigation review board at the William Beaumont Army Medical Center, El Paso, Tex. Domestic swine weighing 10 to 20 kg were initially sedated with an intramuscular injection of ketamine hydrochloride before induction with intramuscular fentanyl citrate and droperidol. After an aural intravenous line was started, the animals were given intravenous pentathol sodium. General anesthesia was maintained with 1% to 3% halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) to effect, 55% to 60% nitrous oxide, and 40% to 45% oxygen.

The animals were divided into two groups: intravenous and intraosseous. There were six runs per group, for a total of 12 runs. Two of the animals were used in both the intravenous and intraosseous trials at two separate times, for a total of 10 animals. All animals were treated in a humane fashion and recovered with adequate pain control after the procedure.

After intubation, all animals were continuously monitored with electrocardiography. All animals underwent a surgical procedure for placement of both a femoral artery catheter and a 7F Swan-Ganz catheter into the femoral vein. The venous catheter tip was advanced with continuous pressure monitoring through the heart to the pulmonary artery, where wedge pressures were identified. The intravenous group had a long intravenous catheter placed into the right femoral vein next to the Swan-Ganz catheter for delivery of dobutamine hydrochloride and isoproterenol hydrochloride. Both catheters were secured at their entry site with nylon suture. The intraosseous group had a bone marrow biopsy needle placed into the left tibial bone marrow space at the upper medial aspect of the tibia just below the tubercle. Placement into the bone marrow space was confirmed by both aspiration of bone marrow and demonstration of visible bone spicules. A pressure transducer was attached to the femoral arterial catheter to measure diastolic, systolic, and mean arterial pressures. Cardiac outputs were measured by the thermal dilution technique (American Edwards Laboratory Cardiac Output Computer, American Edwards Laboratory, Santa Ana, Calif). Intravenous and intraosseous infusions were delivered with Harvard infusion pumps.

Both dobutamine and isoproterenol were delivered at rates of 20 µg/kg per minute intraosseously or intravenously. Heart rate, mean

Accepted for publication July 2, 1990.

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The opinions expressed are those of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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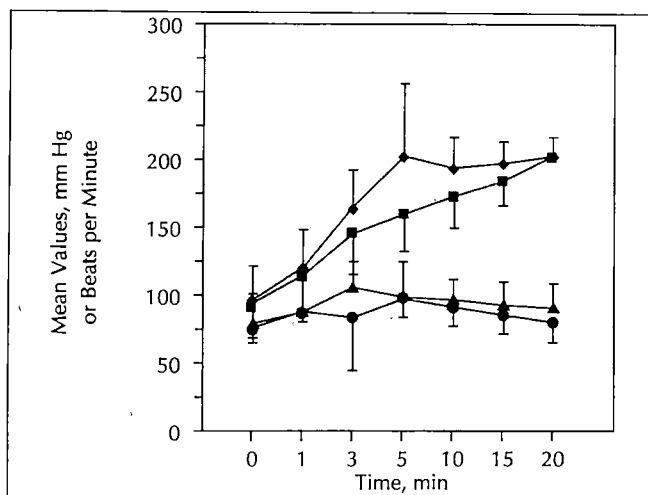


Fig 1.—Effect of dobutamine hydrochloride on heart rate (in beats per minute) and arterial pressure (in millimeters of mercury). Mean values with 1 SD are given for both variables. Circles indicate arterial pressure with intravenous infusion; triangles, arterial pressure with intraosseous infusion; squares, heart rate with intravenous infusion; and diamonds, heart rate with intraosseous infusion.

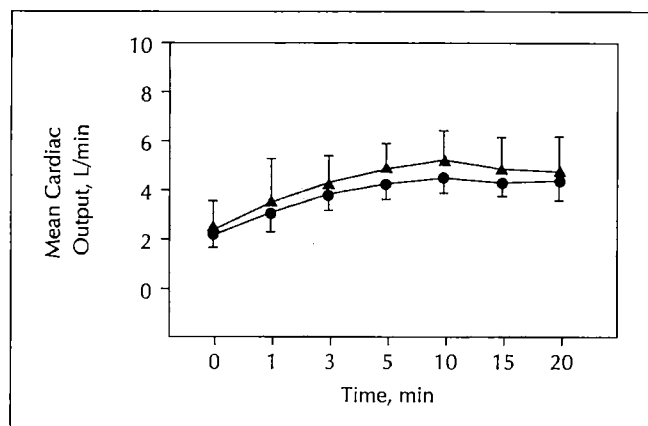


Fig 2.—Effect of dobutamine hydrochloride on cardiac output. Values are means with 1 SD. Circles indicate intravenous infusion; triangles, intraosseous infusion.

arterial pressure, and cardiac output (average of three trials) were measured at 0, 1, 3, 5, 10, 15, and 20 minutes. Zero time data were recorded immediately before the onset of infusion. During all trials, the drug infusions were flushed to the ends of the tubing (to the hub of the bone biopsy needles or intravenous catheters).

For each animal, dobutamine was delivered first. The isoproterenol infusion trials were performed when both heart rate and blood pressure returned to within 5% of their original baseline values or after 30 minutes, whichever occurred first.

RESULTS

In the dobutamine studies, baseline values (mean \pm 1 SD) of heart rate (intraosseous group vs intravenous group, 91 ± 24 vs 95 ± 24 beats per minute), arterial pressure (intraosseous group vs intravenous group, 75 ± 8 vs 78 ± 20 mm Hg), and cardiac output (intraosseous group vs intravenous group, 2.2 ± 0.5 vs 2.4 ± 1.0 L/min) were statistically similar ($P > .10$). The results of the heart rate, arterial pressure, and cardiac output determinations at each time interval are illustrated in Figs 1 and 2. The values for each variable at each time point were compared with use of a paired t test. All results were similar between the intraosseous and intravenous groups, with the exception of heart rate at 5 minutes. Heart rate for the intraosseous group

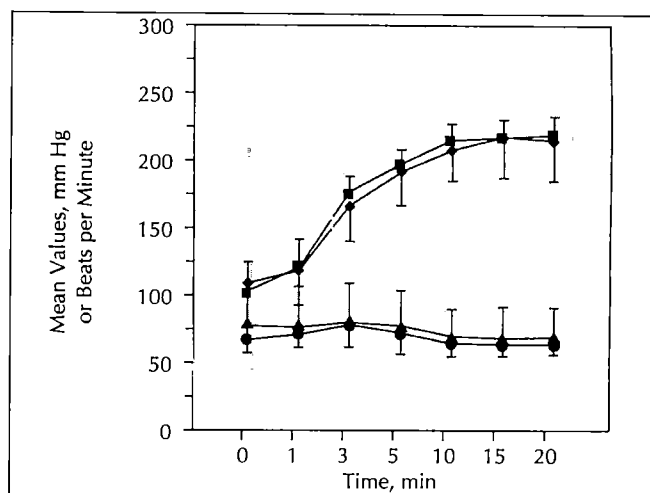


Fig 3.—Effect of isoproterenol hydrochloride on heart rate (beats per minute) and arterial pressure (in millimeters of mercury). Mean values with 1 SD are given for both variables. See Fig 1 for explanation of symbols.

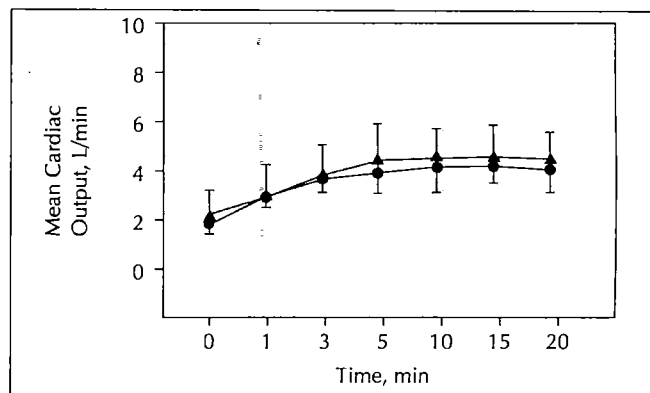


Fig 4.—Effect of isoproterenol hydrochloride on cardiac output. Values are means with 1 SD. Circles indicate intravenous infusion; triangles, intraosseous infusion.

at 5 minutes was greater than that for the intravenous group without apparent explanation. Moreover, statistically significant ($P < .05$) increases were noted in heart rates and cardiac outputs as a result of dobutamine infusions. Both heart rate and cardiac output essentially doubled by 20 minutes whether dobutamine was infused via a vein or into the bone marrow. Arterial pressure did not demonstrate a significant difference from its baseline in either group, regardless of the route of administration.

In the isoproterenol studies, baseline values of heart rate (intravenous group vs intraosseous group, 101 ± 20 vs 107 ± 22 beats per minute), arterial pressure (intravenous group vs intraosseous group, 65 ± 8 vs 77 ± 23 mm Hg), and cardiac output (intravenous group vs intraosseous group, 1.7 ± 0.4 vs 2.1 ± 0.9 L/min) were statistically similar ($P > .10$). The results of the heart rate, arterial pressure, and cardiac output determinations at each time interval are illustrated in Figs 3 and 4. The values for each variable at each time point were compared with use of a paired t test. All results were similar between the intraosseous and intravenous groups. In addition, statistically significant ($P < .05$) increases were noted in heart rates and cardiac outputs as a result of isoproterenol infusions. Both heart rate and cardiac output approximately doubled by 20 minutes whether isoproterenol was infused by the intravenous or the intraosseous route. Arterial pressure, on the other hand, showed no clear trend in either group.

COMMENT

In this study, the infusions of dobutamine and isoproterenol through the bone marrow were as effective as intravenous infusions of these drugs. Our data suggest that the emergency intraosseous infusion of dobutamine and isoproterenol may be successfully employed should achievement of intravenous access be delayed.

With our present data, the list of drugs for the treatment of cardiac arrest that have been studied with the use of intraosseous infusion continues to expand and now includes epinephrine, sodium bicarbonate, hypertonic glucose, dopamine, dobutamine, and isoproterenol. With the exception of sodium bicarbonate,²¹ studies have involved observations made in animals under normal hemodynamic conditions. Although sodium bicarbonate was effectively administered by bone marrow infusion during circulatory collapse and cardiopulmonary resuscitation, the available animal data do not guarantee that the other drugs will be effective under such dire circumstances.

In addition, clinicians who employ intraosseous infusions must keep in mind that this method is simply a temporary measure until reliable and adequate intravenous infusion routes are established. Intraosseous infusion should be discontinued at the first available opportunity. Osteomyelitis has been cited as a serious complication of intraosseous infusion. In his study of almost 1000 intraosseous infusions, Heinild et al¹¹ documented osteomyelitis in 10% of hypertonic glucose infusions. Osteomyelitis is primarily associated with prolonged continuous infusion, especially longer than 24 hours.^{10,11,18} A review by Rossetti et al²³ revealed that among 4270 cases of intraosseous infusions in humans, only 27 cases (0.6%) of osteomyelitis were reported. Osteomyelitis usually occurred with prolonged intraosseous infusion at a single site and in the bacteremic patient. The risk of osteomyelitis from an intraosseous line, therefore, should be weighed against the risks of impending or untreated cardiovascular collapse if immediate intravascular access is not obtained. Although the possibility of fat embolism has also been considered, it has not been reported to result from tibial infusions in humans, probably due to the relative lack of fat in the bone marrow of children.²⁴

Our data provide further substantiation that intraosseous infusion should be regarded as an effective emergency technique for the administration of emergency drugs and fluids, especially dobutamine and isoproterenol.

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Effectiveness of Growth-Promoting Therapies

Comparison Among Growth Hormone, Clonidine, and Levodopa

Cecilia Volta, MD; Lucia Ghizzoni, MD; Gaetano Muto, MD; Raffaella Spaggiari, MD;
Raffaele Virdis, MD; Sergio Bernasconi, MD

● The ability of growth hormone, clonidine, and levodopa to stimulate growth was compared in short and slowly growing children randomly assigned to different treatment regimens for 6 months. There were 10 children in each group, and 10 additional subjects served as controls. Growth hormone improved mean height velocity, height velocity SD score, and height SD score. The mean height velocity and height velocity SD score were significantly increased by clonidine, while levodopa only enhanced the mean height velocity SD score of the treated children. Moreover, in nine patients (90%) receiving growth hormone, two (20%) receiving clonidine, and one (10%) receiving levodopa, the height velocity was raised by more than 2 cm/y. The increments in height velocity and height SD score were greatest in the growth hormone group. Clonidine induced an increase in height velocity significantly different from that in control children only. In the control group, there was a significant reduction of height SD score with time.

(AJDC. 1991;145:168-171)

In 1981, Rudman et al¹ showed that short-term growth hormone (GH) treatment was effective in improving height velocity (HV) in a group of short and slowly growing children with normal pituitary function. Since then several other studies²⁻⁷ have demonstrated that a high percentage of short normal children show a sustained clinical benefit from GH therapy. However, the important factors in predicting the response to treatment have not yet been clearly defined.⁸

Increasing knowledge of the neuroendocrine mechanisms regulating GH secretion has led to the use of substances known to acutely stimulate GH release from the pituitary, such as clonidine⁹⁻¹¹ and levodopa,^{12,13} for the treatment of short stature. The results of these studies are extremely discordant, probably due to the heterogeneity of clinical features and the small number of subjects studied.

To evaluate and compare the growth-promoting effects

of GH, clonidine, and levodopa, we analyzed the growth response to long-term administration of these agents in a group of short children with the same auxological features. The results obtained were compared with those in a group of subjects receiving no medication.

MATERIALS AND METHODS

Forty children (eight girls and 32 boys) with short stature were evaluated at the Growth Clinic of the Department of Pediatrics of the University of Parma, Italy. Inclusion criteria for entry in the study are reported in Table 1. The value of -0.8 for HV SD score (HVSDS) was chosen because it is the lowest value at which prepubertal children can grow at the third percentile.¹⁴

Patients were randomly assigned to the following groups: group 1 (n = 10), no medication; group 2 (n = 10), levodopa (Larodopa, LaRoche Inc, Basel, Switzerland), 60 mg/kg per day by mouth three times per day up to 25 kg, with a constant dosage of 1500 mg/d thereafter, for 6 months; group 3 (n = 10), clonidine (Catapresan, Boehringer, Mannheim, Germany), 75 µg/m² by mouth twice per day, one third in the morning and two thirds in the evening, for 6 months; and group 4 (n = 10), GH (Somatomorm, KabiVitrium Inc, Stockholm, Sweden), 13 IU/m² per week, subdivided in six subcutaneous daily injections, for 6 months.

Informed consent was obtained from parents, and the study was approved by the ethical committee of the Department of Pediatrics of the University of Parma. Standard auxological assessment (height, weight, height velocity, and pubertal staging) was performed at 3-month intervals for 6 months. Kidney, liver, and thyroid function was checked in all children at baseline, and, in the groups under treatment, after 3 and 6 months; in addition, an oral glucose tolerance test and glycosylated hemoglobin evaluation were performed before and after treatment in group 4 only. A roentgenogram of the left hand for bone age evaluation was performed at baseline and at the end of the study period.

Height was measured with a wall-mounted Harpenden stadiometer; bone age was determined by an experienced examiner using the standards of Greulich and Pyle.¹⁵ The HV before the study was calculated based on measurements taken in the preceding year and expressed as the HVSDS corrected for bone age. An increase in HV greater than 2 cm/y was considered significant, because this approximates 2 SDs of the variation that occurs in whole-year HVs in normal prepubertal children.¹⁶ Serum GH, levothyroxine, triiodothyronine, thyroid-stimulating hormone, free thyroxine, and free triiodothyronine levels were measured as previously described.^{13,17}

All results are expressed as mean ± SD. For statistical analysis, we used the paired *t* test for comparisons within groups and the Newman-Keuls test for multiple comparisons among independent groups of data; correlations were evaluated by linear regression analysis.

Accepted for publication August 6, 1990.

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Presented in part at the Third Joint Meeting of the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrinology Society, Jerusalem, Israel, October 31, 1989.

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Table 1.—Inclusion Criteria for Entry in the Study

Birth weight appropriate for gestational age
 No evidence of systemic diseases, malnutrition, dysmorphic syndromes, or psychosocial disturbances
 Tanner stage 1 of pubertal development
 Height SD score < -2
 Whole-year height velocity SD < -0.8
 Growth hormone response to pharmacological stimuli $>10 \mu\text{g/L}$ (insulin hypoglycemia, 0.1 U/kg intravenously, or clonidine, 100 $\mu\text{g/m}^2$ by mouth)
 Normal thyroid function

RESULTS

At inclusion, mean chronological age, bone age, HV, height SD score (HSDS), and HVSDS corrected for bone age were similar in all groups (Table 2). There were also no differences in mean midparental height (group 1, 160.4 ± 4 cm; group 2, 157.5 ± 4 cm; group 3, 157.3 ± 6 cm; and group 4, 157.9 ± 6 cm).

Results at the end of the study period are shown in Table 2 and Fig 1 and can be summarized as follows:

Group 1.—The HV and HVSDS did not significantly change in the 6-month follow-up. However, there was a significant decrease in the HSDS (-2.3 ± 0.4 vs -2.4 ± 0.4 , $P < .05$).

Group 2.—Levodopa administration significantly improved the mean HVSDS only (-0.9 ± 1.1 vs -2 ± 0.8 , $P < .05$); the mean HV and HSDS were similar to the baseline values. Only one patient had an increase in HV greater than 2 cm/y (from 3.6 to 7 cm/y).

Group 3.—The mean HV and HVSDS were significantly increased by clonidine therapy (5 ± 1 vs 3.8 ± 1 cm/y, $P < .005$; and -1.1 ± 0.9 vs -2.4 ± 1 , $P < .005$, respectively). However, only two patients had an improvement in HV (from 4.6 to 6.8 cm/y and from 3 to 5.8 cm/y).

Group 4.—Administration of GH significantly improved HV (6.8 ± 1 vs 3.9 ± 0.6 cm/y, $P < .001$) and HVSDS (1.9 ± 1.3 vs -1.9 ± 0.8 , $P < .001$) as well as HSDS (-2.8 ± 0.5 vs -3.1 ± 0.6 , $P < .01$). Nine patients (90%) had an increase in HV greater than 2 cm/y.

The bone age/chronological age ratio did not change in any group, and all the children remained prepubertal throughout the study. When the baseline individual HV, HVSDS, and HSDS values of all subjects were plotted with respect to the corresponding values after therapy, no correlation was found.

Comparisons among independent groups after 6 months of either therapy or clinical follow-up showed that the mean posttreatment HV was significantly higher ($P < .05$) in group 4 than in all other groups (6.8 ± 1 [group 4] vs 3.5 ± 0.6 [group 1], 4.5 ± 1.3 [group 2], and 5.1 ± 1.1 [group 3] cm/y), and the value in group 3 was significantly higher ($P < .05$) than in group 1. Figure 2 shows the increment in HV. Growth hormone therapy resulted in an improvement in HV greater than that in all other groups (2.9 ± 0.9 [group 4] vs -0.16 ± 0.9 [group 1], 0.6 ± 1.6 [group 2], and 1.2 ± 0.8 [group 3] cm/y), while clonidine induced an increase in HV significantly greater than that in control children only. Levodopa seems not to be able to induce remarkable improvements in HV.

The changes in HVSDS and HSDS are also shown in Fig 2. The change in HVSDS was significantly greater ($P < .05$) in group 4 (3.9 ± 1.4) than in all other groups (-0.13 ± 1 [group 1], 0.88 ± 1 [group 2], and 1.25 ± 0.7 [group 3]), and the changes in HVSDS were significantly greater in groups 2 and 3 than in group 1. The change in HSDS was significantly greater in group 1 (-0.09 ± 0.05) than in all other

Table 2.—Auxological Data Before and After the Study Period

	Group			
	Control	Levodopa	Clonidine	Growth Hormone
No. of subjects	10	10	10	10
Chronological age, y				
Before study period	9.4 \pm 2.1	9.7 \pm 1.8	8.9 \pm 2.1	10.9 \pm 1.7
After study period	9.9 \pm 2.1	10.2 \pm 1.8	9.4 \pm 2.1	11.4 \pm 1.7
Bone age, y				
Before study period	6.89 \pm 2.1	7.70 \pm 2.2	6.51 \pm 2.1	8.75 \pm 1.9
After study period	7.88 \pm 1.8	8.21 \pm 2.4	7.12 \pm 1.9	9.57 \pm 1.9
Height velocity, cm/y				
Before study period	3.7 \pm 1.2	3.9 \pm 0.6	3.8 \pm 1.0*	3.9 \pm 0.6*
After study period	3.5 \pm 0.6	4.5 \pm 1.3	5.0 \pm 1.1*	6.8 \pm 1.0*
Height SD score				
Before study period	-2.3 \pm 0.4*	-2.5 \pm 0.4	-2.6 \pm 0.6	-3.1 \pm 0.6*
After study period	-2.4 \pm 0.4*	-2.5 \pm 0.4	-2.5 \pm 0.7	-2.8 \pm 0.5*
Height velocity SD score corrected for bone age				
Before study period	-2.4 \pm 1.4	-2 \pm 0.8*	-2.4 \pm 1.0*	-1.9 \pm 0.8*
After study period	-2.5 \pm 0.9	-0.9 \pm 1.1*	-1.1 \pm 0.9*	1.9 \pm 1.3*

* $P < .05$ for before vs after the study period.

groups (0.001 ± 0.1 [group 2], 0.08 ± 0.1 [group 3], and 0.23 ± 0.1 [group 4]), confirming that the HSDS worsened in the untreated children, and the change in HSDS was significantly greater in group 4 than in groups 2 and 3.

Thyroid, kidney, and liver function and oral glucose tolerance test results were normal in all subjects. The only side effects reported were slight transitory sleepiness in four children receiving clonidine and occasional nausea and vomiting in six patients receiving levodopa.

COMMENT

In recent years, the virtually unlimited supply of recombinant GH has led to renewed interest in treating short children who do not fulfill the classic criteria of GH deficiency. Even if the results of many studies seem encouraging, the long-term safety and efficacy of GH treatment are still unknown. Moreover, the ethics of treating disease-free children are still under debate, and the high cost of the drug places a heavy economic burden on the family and/or society.^{18,19}

These problems together with expanded knowledge of the neuroregulatory mechanisms of GH secretion have led to the use of alternative agents, such as clonidine and

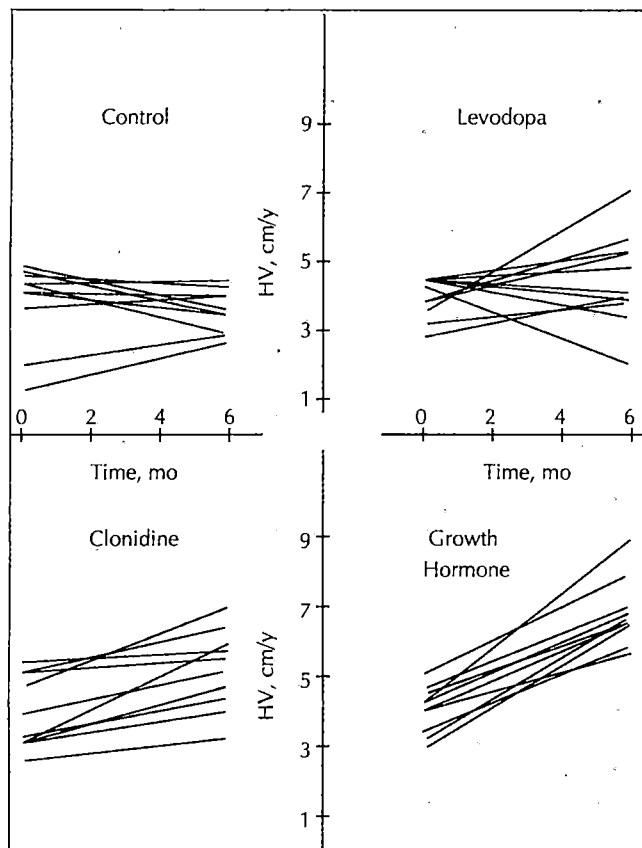


Fig 1.—Individual height velocities (HVs) of children in groups 1 (no medication), 2 (levodopa), 3 (clonidine), and 4 (growth hormone).

levodopa, that are able to stimulate GH production from the pituitary. The mechanism of action of these drugs is not yet completely clear. There is indirect evidence that the GH secretion induced by levodopa is due to the release of GH releasing hormone, while clonidine seems to predominantly act through inhibition of the somato-statinergic tone.²⁰

Several trials with these agents have been conducted in different subpopulations of short normal children. However, to our knowledge, no studies have examined the different growth-stimulating efficacy of these drugs in children with similar clinical and auxological features. For this reason we compared the ability of GH, clonidine, and levodopa to enhance growth in a homogeneous group of short and slowly growing children.

The findings of the present study indicate that GH is effective in improving the growth of short normal children. The administration of levodopa for 6 months did not induce positive changes in the auxologic parameters analyzed, while the results obtained with GH were intermediate between those with GH and levodopa. However, despite the absence of remarkable improvements, both clonidine and levodopa were able to prevent the reduction of HSDS that occurred in the control group.

The results summarized above demonstrate that GH was the most effective growth-promoting agent we used. This observation is in agreement with studies in which a high percentage of short children receiving short-term GH therapy had an improvement in both HV and HSDS.¹⁻⁷ The lack of correlation between pretreatment and post-treatment values of all the auxologic parameters analyzed indicates that these factors were not important in predicting response to treatment. Therefore, a short-term ther-

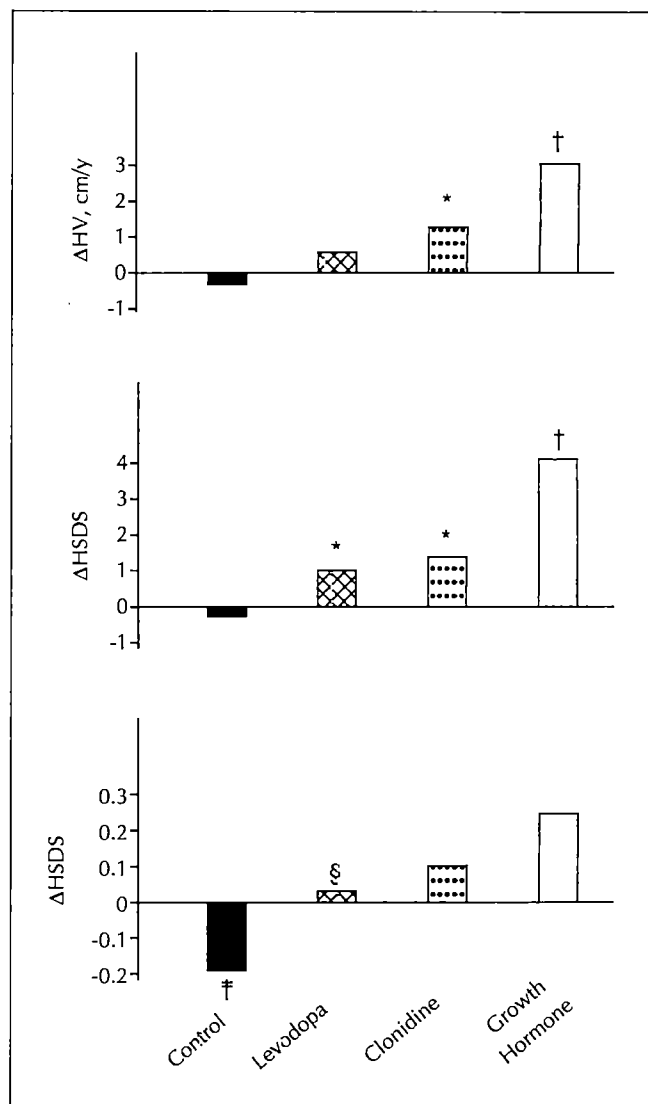


Fig 2.—Changes in height velocity (Δ HV), HV SD score (Δ HVSDS), and height SD score (Δ HSDS). Asterisk indicates $P < .05$ compared with the control group; dagger, $P < .05$ compared with the control, levodopa, and clonidine groups; double dagger, $P < .05$ compared with the levodopa, clonidine, and growth hormone groups; and section mark, $P < .05$ compared with the growth hormone group.

apeutic trial with GH seems to be the only way to identify the children who might benefit from this therapy.^{21,22}

Huseman¹² reported evidence for dopaminergic stimulation of growth in GH-deficient subjects and in children with intrauterine growth retardation, microcephaly, and psychomotor delay. In addition, it has been shown that levodopa potentiates the effects of GH treatment in some children with growth hormone deficiency.²³ The results we obtained treating short normal children with levodopa are not as encouraging as those mentioned above. Only one child, in fact, had an improvement in HV greater than 2 cm/y. It should be pointed out, however, that the heterogeneity of clinical characteristics of the patients examined in the different studies makes comparisons unsuitable.

The potential usefulness of clonidine as a growth-promoting agent in the treatment of non-GH-deficient short stature has been shown in three studies. The most encouraging study reported on 16 prepubertal children from San Salvador, El Salvador, who were treated with a

single nightly dose of clonidine, 0.15 mg/m², for 1 year.¹⁰ All 16 children had a rise in HV during treatment. The other two reports were by Pintor et al,^{9,24} who treated 34 short normal children with clonidine, 0.1 mg/m² daily in two doses. The majority of children responded to the treatment regimen, although HV increased by more than 2 cm/y in only 21 subjects. In contrast to these studies, Pescovitz and Tan¹¹ found no sustained increases in GH production or improvements in HV in a placebo-controlled trial with administration of a single daily dose of clonidine, 0.1 mg/m².

In the present investigation, despite the improvement in mean HV and HVSDS, clonidine raised HV by more than 2 cm/y in only two children, results that approximate those of Pescovitz and Tan.

The most significant differences among these studies are those in patient selection and clonidine dosing. This is why it was important to test the efficacy of these drugs in subjects with similar clinical characteristics randomly assigned to different treatment regimens.

The absence or inadequacy of controls is a major limit of many reports, particularly when the purpose of the study is the evaluation of drug efficacy. In our study the follow-up of the control children showed a significant reduction in HSDS with time, probably related to the persistence of low HV throughout. This finding is partially at variance with the results of Pescovitz and Tan¹¹ in children treated with placebo. However, the baseline HV in this group of children treated with placebo was higher than in our patients, which might explain the divergent growth patterns of the two groups. The fact that HSDS was not reduced in the children treated with levodopa and clonidine indicates that these drugs did positively affect growth; at least growth did not deteriorate in these subjects, as it did in untreated subjects.

In conclusion, GH appears to be the most effective drug tested in this study in promoting growth in short normal children with the above-mentioned auxological features. However the effect on growth showed by clonidine and, to a lesser degree, by levodopa, although not sufficient to counsel treatment with these drugs, could lead to new ways of treatment, such as with newer GH-stimulating substances.

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Age-Related Patterns of Thyroid-Stimulating Hormone Response to Thyrotropin-Releasing Hormone Stimulation in Down Syndrome

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● Thyroid function in subjects with Down syndrome was studied using the thyrotropin-releasing hormone test. Forty-seven infants and children with Down syndrome were investigated. Ages ranged from 1 month to 7 years; there were 26 boys and 21 girls. Fourteen of the subjects with Down syndrome who had an exaggerated thyroid-stimulating hormone response to thyrotropin-releasing hormone stimulation had two or more annual follow-up tests. The remaining 33 subjects who only underwent one thyrotropin-releasing hormone test were compared with 22 age-matched controls (11 boys and 11 girls). Mean basal thyroxine 4 and triiodothyronine 3 values were in the normal ranges. All thyroid antibody titers were negative. Mean basal thyroid-stimulating hormone levels of subjects with Down syndrome were significantly higher than those of controls for all ages, even though there was a decline in thyroid-stimulating hormone levels in both groups. Peak thyroid-stimulating hormone response levels were significantly greater in the subjects with Down syndrome than in the controls. Longitudinal study of the 14 children with Down syndrome with an exaggerated thyroid-stimulating hormone response showed that the response remained exaggerated until the third year of life, when it declined to normal levels. Thyroid dysfunction during the growth spurt of infancy or delayed maturation of the hypothalamic pituitary thyroid axis are proposed mechanisms.

(AJDC. 1991;145:172-175)

An increased prevalence of disorders of the hypothalamic-pituitary thyroid axis in children with Down syndrome has been described. Autoimmune thyroiditis in cases of pubescent and postpubescent Down syndrome is well known.¹⁻⁴ The prevalence of congenital hypothyroidism in neonates with Down syndrome has been reported to be 28 times greater than that in normal neonates.⁵ Higher mean basal thyroid-stimulating hormone

(TSH) levels in patients with Down syndrome compared with controls has been shown to occur throughout the age spectrum, including infancy. This phenomenon has been termed *thyroid dysfunction*.^{6,7} However, these high mean basal TSH levels are accompanied by normal mean thyroxine (T_4) and triiodothyronine (T_3) levels. The meaning of the high basal TSH levels in association with normal T_4 and T_3 levels in patients with Down syndrome has yet to be explained.

Infants with Down syndrome with high TSH levels have been shown to be smaller than those with lower TSH levels.⁸ This observation has been noted in infancy, mainly before age 4 years. Some children with hypothalamic-pituitary disorders have high basal TSH levels and an exaggerated TSH response to the administration of exogenous thyrotropin-releasing hormone (TRH) in the presence of normal T_3 and T_4 levels.^{9,10} The present study, using the TRH stimulating test, was undertaken to further elucidate thyroid dysfunction in infants and children with Down syndrome.

PATIENTS AND METHODS

Forty-seven infants and children with Down syndrome were included in the study. Chromosomal analysis showed that a trisomy 21 was present in 45 children; one other case was a translocation and another was a mosaic. Ages ranged from 1 month to 7 years; there were 26 girls and 21 boys. Thirty-seven of the patients were from the Jerusalem (Israel) Child Development Center to which all infants with Down syndrome born in Jerusalem are referred. Ten patients were from the Rehovot area of Israel. Initially, the patients were included as they came for routine follow-up; they ranged in age from 1 month to 7 years. However, as new infants were born they were studied within 3 months of birth; consequently, there were more infants in the youngest age category. All the infants included in the study were born within 3 weeks of term, all were in good health, and none had clinical goiter.

Patients were examined after an overnight fast or, in infants, 4 hours after their early morning feeding. The TRH stimulation test was performed by injecting an intravenous 4- μ g/kg bolus of synthetic TRH (Roche, F. Hoffman La Roche Ltd, Basle, Switzerland); serum TSH levels were determined before injection and 15, 30, and 60 minutes after injection. The higher of the 15 and 30 minute values was designated as the peak value. Total T_4 and T_3 levels were measured in unextracted serum by radioimmunoassay (Seralute Ames Co, Elkhart, Ind; T_3 RIA Kit, Amersham, Arlington Heights, Ill). Serum TSH levels were measured by radioimmunoassay¹¹ with a sensitivity of 0.5 to 1.0 mU/L.

Antibody titers to thyroglobulin and thyroidal microsomal antibodies were measured by immunofluorescence. The Jerusalem

Accepted for publication May 18, 1990.

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Table 1.—Thyroxine (T₄) Values and Levels of TSH Response to TRH Injection in Patients With Down Syndrome and Controls by Age Groups*

Group	No.	T ₄ , nmol/L	Basal TSH, mU/L†	Peak TSH, mU/L (15 or 30 min)‡	TSH, mU/L (60 min)§
Overall					
Down syndrome	3	126 ± 35	7.3 ± 6.9	25.8 ± 11.4	18.2 ± 11.4
Control	22	142 ± 19	2.5 ± 1.8	14.7 ± 5.7	10.8 ± 5.4
<1 y					
Down syndrome	19	126 ± 42	10.2 ± 7.7	30.5 ± 11.3	23.2 ± 13.5
Control	7	138 ± 19	4.0 ± 2.3	18.0 ± 4.2	15.5 ± 5.3
1 to 3 y					
Down syndrome	7	127 ± 23	4.2 ± 3.9	23.9 ± 8.1	15.3 ± 4.4
Control	6	133 ± 19	2.3 ± 1.1	17.5 ± 5.4	10.9 ± 3.9
3 to 7 y					
Down syndrome	7	116 ± 22	2.7 ± 0.6	14.9 ± 4.8	9.6 ± 3.6
Control	9	153 ± 21	1.3 ± 0.8	9.0 ± 2.4	5.9 ± 1.7

*Numbers are means ± SDs. TSH indicates thyroid-stimulating hormone; and TRH, thyrotropin-releasing hormone.

†Using analysis of variance (ANOVA), $f = 4.1$; $P < .05$.

‡Using ANOVA, $f = 11.9$; $P < .001$.

§Using ANOVA, $f = 4.0$; $P < .05$.

and Rehovot laboratories used the same kits and standard measurements. The normal adult ranges for the laboratory values are as follows: T₄, 59 to 154 nmol/L; T₃, 1.23 to 3.1 nmol/L; and TSH, 0.5 to 6 mU/L. A peak TSH response of above 20 mU/L is classified as exaggerated. Fisher's criteria¹² were used to diagnose hypothyroidism as a function of age. The values were as follows: from 1 to 12 months, T₄, 80 to 198 nmol/L; T₃, 1.6 to 3.4 nmol/L; and TSH, 0.5 to 6.5 mU/L; from 1 to 6 years, T₄, 68 to 171 nmol/L; T₃, 1.5 to 3.4 nmol/L; and TSH, 0.6 to 6.3 mU/L; and from 7 to 12 years, T₄, 62 to 160 nmol/L; T₃, 1.3 to 3.2 nmol/L; and TSH, 0.6 to 6.3 mU/L. The TSH responses to TRH stimulation in the infants with Down syndrome were compared with those of the controls.

An age-matched control group of 22 infants and children (11 boys and 11 girls) was obtained from the Pediatric Endocrinology Departments of the Jerusalem and Rehovot Hospitals. These were children who, during the period of the study, underwent the TRH test for various clinical reasons and in whom no subsequent biologic or endocrine abnormality was found. Thirty-three of the children with Down syndrome who underwent only one TRH test were compared with the controls. The children with Down syndrome and the controls were grouped according to age.

There were insufficient numbers of subjects tested to group by year, so the grouping was as follows: younger than 1 year; 1 to 3 years of age; and older than age 3 years. The remaining subgroup of 14 children with Down syndrome who had an initial exaggerated response to TRH stimulation was analyzed separately. All 14 patients had a TRH test performed again after approximately 1 year, and six patients had three annual TRH tests performed. Eighteen of the tests were performed on children younger than 1 year, 11 on children between ages 1 and 3 years, and five on children older than 3 years.

For statistical analysis, a repeated-measures analysis of variance (ANOVA) was performed to examine differences between children with Down syndrome and controls at varying age groups.^{13,14} For the group of 14 children with Down syndrome who had follow-up repeated TRH tests performed, Duncan's Multiple Range Test was used. This was used to partition the effects of age within subject variation and across subject variation in TSH.

RESULTS

Mean T₄ and T₃ values were within the normal range in both the Down syndrome and control groups. All thyroid antibody study results were negative. Using Fisher's criteria,¹² none of the infants with Down syndrome had T₄ levels sufficiently low to be designated clearly as hypothyroid. Table 1 shows T₄ values in relation to basal, peak, and 1-hour TSH levels in subjects with Down syndrome and controls. Repeated-measures ANOVA showed that mean

Table 2.—Basal and Peak TSH Levels in a Group of 14 Patients With Down Syndrome Studied Longitudinally*

	Age, y		
	<1†	1-3†	3-7
No. of tests	11	18	5
Basal TSH level, mU/L‡	8.1 ± 4.9	6.8 ± 3.9	2.1 ± 1.0
Peak TSH level, mU/L§	35.9 ± 7.1	36.4 ± 10.1	24.3 ± 13.6

*Unless otherwise indicated, numbers are means ± SDs. TSH indicates thyroid-stimulating hormone.

†Values for patients younger than 1 year and between 1 and 3 years are not statistically different.

‡Using Duncan's Multiple Range Test, $f = 3.45$ and $P < .05$.

§Using Duncan's Multiple Range Test, $f = 3.96$ and $P < .05$.

basal TSH levels of subjects with Down syndrome were significantly higher than those of age-matched controls ($f = 4.1$; $P < .05$). The peak TSH response was significantly higher in the Down syndrome population than in the control group ($f = 11.9$; $P < .001$). The mean 1-hour TSH level was also significantly higher in the subjects with Down syndrome than in the controls ($f = 4.0$; $P < .05$). This difference between patients with Down syndrome and controls held true for all age categories, even though the basal and peak TSH levels of the children with Down syndrome declined to levels that would be considered normal for age. The subgroup of 14 subjects with Down syndrome who had an initial exaggerated TSH response to TRH stimulation was studied longitudinally.

Duncan's Multiple Range Test (Table 2) showed a significant difference of basal TSH and peak TSH levels between the two younger age groups compared with the oldest age category ($P < .05$). The mean peak TSH response remained at a level of 36.4 mU/L until the third year, after which it declined to approximately normal levels.

COMMENT

The concentrations of serum thyroid hormones vary with age, and norms as a function of age have been derived.¹² Our baseline results were compared with these norms as well as with levels in the controls used in the study. Although the number of controls in the present

study was small because the TRH test is not a routine procedure, when control group peak TSH values were compared with those of a larger study, the values were compatible.¹⁵ For children younger than 1 year, our control group peak TSH level was 18 mU/L compared with 17 mU/L for a larger study group; between 1 and 3 years, 17.5 mU/L compared with 14.1 mU/L; and between 3 and 6 years, 9.0 mU/L compared with 9.7 mU/L.

Using Fisher's criteria,¹² none of our patients with Down syndrome showed clear-cut hypothyroidism, but they had persistently higher basal TSH levels than did normal controls, which were associated with T_4 and T_3 levels appropriate for age. This higher basal TSH level was accompanied by a significantly greater TSH response than in the controls. With increasing age, there was a decline in both basal TSH and peak TSH responses to what could be considered normal levels, although they continued to be higher than those of the controls ($P < .001$). The subgroup of 14 patients with Down syndrome who, on initial testing, had an exaggerated TSH response maintained the exaggerated peak TSH response until the third year of life.

Transiently elevated TSH levels have been observed in premature infants, and are associated with jaundice and respiratory and fetal distress.^{16,17} The cause of the thyroid insufficiency remains unknown. The suggested hypothesis is that it is due to low thyroidal content of iodine in newborn infants and delayed maturation of enzymatic mechanisms of intrathyroidal hormonogenesis. Although none of the infants or children with Down syndrome studied were premature or ill, the above hypothesis could be considered in the etiology. Thyrotropin levels are physiologically high in newborns. Levels decline to normal by age 4 days and even transiently high TSH levels return to normal by age 2 months.¹⁷ In the infant with Down syndrome, prolongation of this physiologically high TSH could be an expression of immaturity of the hypothalamic-pituitary axis. This could result in the secretion of a thyrotropin of low biologic activity, which, in turn, may be an expression of a TRH deficiency.^{18,19} Other hypothalamic factors involved in TSH regulation, such as dopamine or somatostatin levels, may be involved.

Delayed maturation of the hormone somatomedin has been shown to occur in children with Down syndrome,²⁰ with incomplete switching from the fetal form of somatomedin to the growth hormone-related insulin growth factor. With increasing age, the basal TSH and peak TSH responses declined to normal levels. As metabolic needs decline with age, so the biochemical expression of thyroid dysfunction as expressed by TSH measurements improves. Other compensatory mechanisms may come into play, such as the reduction in the pituitary threshold for the feedback of TSH.^{21,22} However, both the basal and peak TSH levels in patients with Down syndrome are consistently higher than those in the controls, which may suggest a different mechanism. The relatively high TSH levels were associated with normal T_4 and T_3 values. Paradoxically high TSH levels in the presence of normal T_4 and T_3 values have been described in a small number of heterogeneous thyroid disorders and have been termed *inappropriate secretion of TSH*.²³ Proposed mechanisms are of peripheral resistance to thyroid hormones or central disorders of TSH secretion. Down syndrome cell membranes are known to have abnormal biochemical, physiologic, and receptor functions.^{24,25} These altered cell membrane properties could possibly have some effect on thyroid hormone receptor functions.

Since the biochemical findings are not of clear-cut hypothyroidism and only of dysfunction that appears to im-

prove with age, one is prompted to ask if there are any clinical implications. Until now, empirical thyroid treatment without clinical or biochemical evidence of hypothyroidism has not proved to be of much value²⁶ and has only created false hopes in the parents of these children. However, it has been shown that children with Down syndrome who are younger than 4 years and who have elevated TSH levels showed growth retardation compared with children with lower TSH levels.⁸

Furthermore, thyroid supplement treatment of a number of infants with hypopituitarism who had normal T_4 values associated with high basal TSH levels and an exaggerated response to TRH led to an increased growth rate during the period of treatment.⁹ Hence, these findings may warrant a trial of thyroid supplementation in those infants with Down syndrome who have high TSH secretion. Ideally, this should be done under double-blind conditions and the follow-up continued until adulthood. The key question remains that even if there is increased short-term growth velocity, is there significant long-term growth improvement? Criteria for improvement in growth and other areas of development will need to be established.

We express our appreciation to the Balint Foundation, London, England, for its financial support.

We also thank J. Gross, MD, and A. Russel, MD, for their advice and encouragement and Shoshana Shanan for her untiring help in doing the testing.

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BOOK REVIEW

Pediatric Intensive Care

2nd ed, edited by Eliezer Nussbaum, 964 pp, \$155, Mount Kisco, NY, Futura Publishing Co, 1989.

This second edition is another entry in the burgeoning area of textbooks addressing topics of the intensive care unit. It bears little similarity to the first edition, being markedly better (and larger) in all respects.

The text is generally well written and covers most subjects in adequate detail for pediatric house officers and practitioners. Its 50 chapters have many excellent features. Most of the pulmonary section is superb. Roentgenographic evaluation of respiratory problems is dealt with nicely in numerous chapters. Several short chapters detail specific entities such as pneumothorax and pleural effusion. These are useful and well-written chapters that provide much valuable information to the bedside clinician. However, some areas are covered only superficially. The chap-

ter on Reye's syndrome is six pages long; it has numerous typographical errors and covers the topic inadequately. Poisoning and drug ingestion also are covered weakly—tricyclic antidepressants and aspirin intoxication are not mentioned, for instance. Details concerning the implementation of technologies such as pulmonary artery catheters, intracranial pressure monitoring, and mechanical ventilation are scarce. Mechanical ventilators are discussed in 5½ pages. Most of the subjects in the section on neurointensive care are described briefly. Finally, issues concerning nursing receive only token attention.

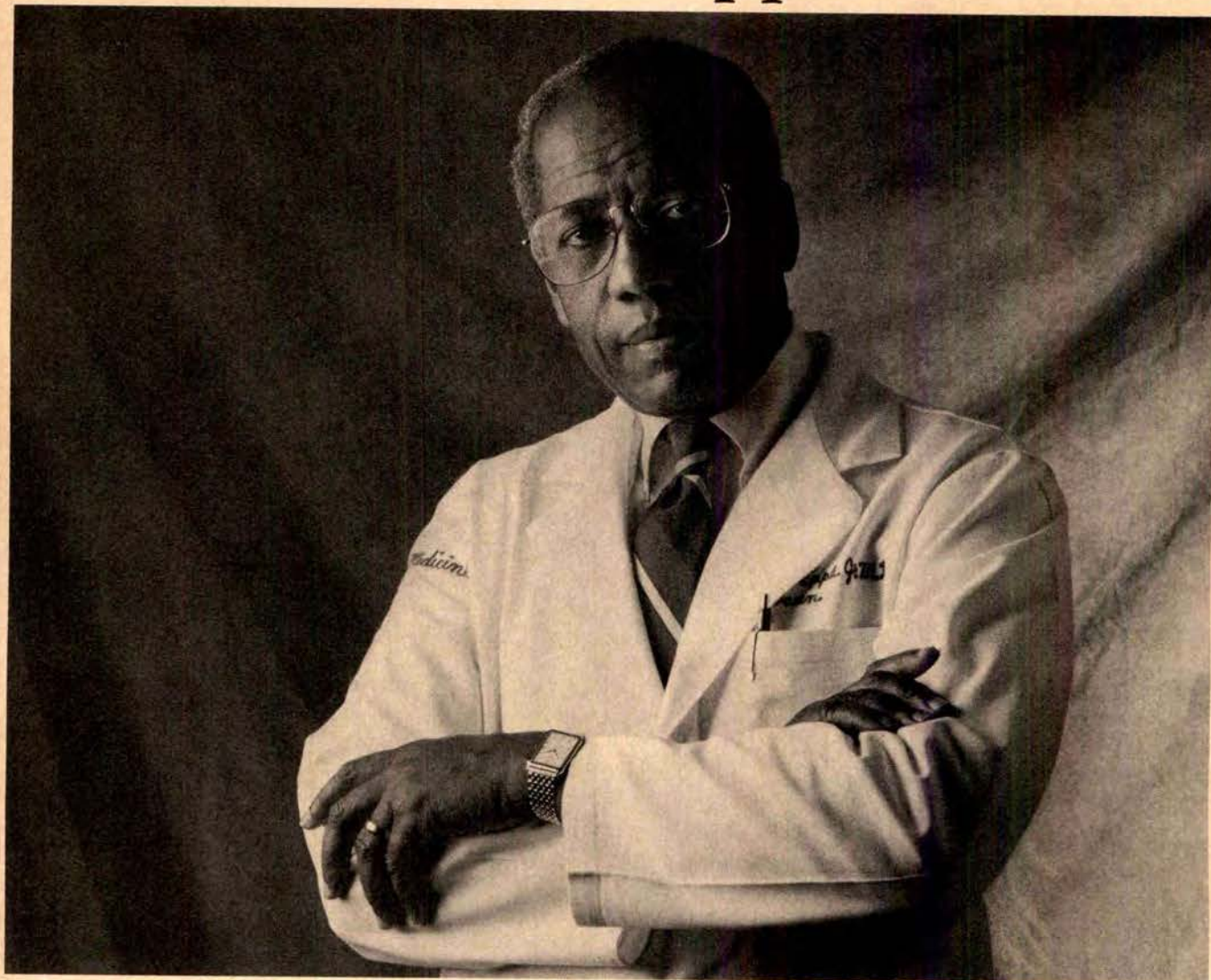
Certain sections of this textbook are excellent. Michael Radetsky has written a beautiful presentation of medical ethics in the pediatric intensive care unit. The entire section is written eloquently; is readable for physicians, nurses, and students; and encapsulates subjects that are often inadequately covered in textbooks of pediatrics or critical care.

The chapter by Drs Royall and Levin on adult respiratory distress syndrome is very good, presenting the perfect level of detail.

How does this book fit into our libraries? Dr Nussbaum has assembled a group of respected authors, and this single-volume text seems a compromise between bedside handbooks and two-volume tomes on the subject. This is not an encyclopedic work and it would be inadequate preparation for subspecialty examinations of critical care. It exceeds the limits of bedside handbooks, and it can be read in several weeks. In short, the textbook succeeds admirably in its purpose, bridging the gap between these two extremes. It should find a welcome spot in many personal libraries.

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Sudden Cardiac Death in Young Athletes

A Review

Francis M. McCaffrey, MD; LCDR David S. Braden, MC, USNR; William B. Strong, MD

Death on the court: Loyola Marymount's Hank Gathers was at the top one minute, the next, he collapsed and lay dying as his mother stood mournfully by him." This was the lead story in the March 12, 1990, issue of *Sports Illustrated* (pp 14-17). *USA Today* (March 6, 1990:1A) carried the story of Hank Gathers' death for 4 days, including the front-page headline, "Athletes at risk: many put health, even life on the line to play." The tragic death of a national sports celebrity gaining front-page coverage is not unusual. Such events hold a morbid fascination and create undue fear among parents, coaches, community leaders, and physicians involved in the care of young athletes. This review will attempt to place sudden cardiac death in a previously asymptomatic young athlete in perspective while providing recommendations for identifying the athlete who may be at risk.

Sudden *unexpected* death (SUD) has been defined as death caused by cardiac arrest up to 6 hours after the initial onset of symptoms or collapse in individuals who have not been previously recognized to have cardiovascular disease.¹ In the following discussion, individuals with known, predisposing cardiac lesions will not be discussed.²⁻⁴ Concern for SUD in athletes is out of proportion to the actual incidence (*Augusta Chronicle*, September 12, 1988:1B), which is estimated to be one to two cases per 200 000 athletes per year.^{5,6} Epstein and Maron⁵ have estimated that five in 100 000 young athletes may have a condition that makes them vulnerable to sudden death, and of those at risk, 10%, or one in 200 000 athletes, will die suddenly and unexpectedly. Between 1983 and 1988, there were less than 60 reported cases of sudden cardiac death among high school athletes, approximately 12 per year in the United States. The incidence of SUD in grade school athletes is less. After excluding trauma, cardiac death is the most frequent cause of sports-related death in young athletes.¹ Few studies are limited to SUD in young athletes.^{1,7-9} However, if one reviews these studies and those involving youth, activity, and SUD, a fairly reproducible group of conditions are reported (Table 1).

HYPERTROPHIC CARDIOMYOPATHY

Whether known as hypertrophic cardiomyopathy (HCM), or by almost 80 other names,¹⁰ including idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy, this disease process is the leading cause of SUD among young athletes.^{2,11,12} Hypertrophic cardiomyopathy is characterized by a hypertrophied but nondilated left ventricle in the absence of systemic disease or left-sided obstruction capable of producing left ventricular hypertrophy (Table 2).^{10,13} Muscular hypertrophy reduces left ventricular chamber size and volume and impairs diastolic filling.^{14,15} Obstruction to left ventricular outflow may occur secondary to the hypertrophy of the subaortic septum^{16,17} and to systolic anterior motion of the mitral valve.¹⁸ In addition to inflow restriction and outflow obstruction, areas of localized hypertrophy other than the septum serve as potential arrhythmogenic foci. Most often, ventricular tachycardia leading to fibrillation is cited as the cause of death,^{19,20} although supraventricular arrhythmias leading to secondary ventricular fibrillation may also occur.²⁰

Prognostic factors for sudden death suggested in patients with HCM are a family history of sudden death,²¹ ventricular tachycardia,²² and a young age at onset of symptoms.^{21,23} For patients known to have HCM, the annual mortality rate ranges from 2% to 3%. However, the annual mortality rate increases to 8% in those patients with a documented episode of ventricular tachycardia.²²

The inheritance of HCM is autosomal dominant with a high degree of penetrance found on echocardiographic examination.^{17,18,24} Therefore, if HCM is confirmed, all first-degree relatives should be examined echocardiographically.

Commonly, there are no symptoms, or the initial symptom is sudden death (Table 2).²² Except for syncope and severe dyspnea,²⁵ symptoms are not predictive of SUD.^{10,13,17,20}

The classic physical examination (Table 2) in patients with HCM includes an increased left ventricular impulse that may

Accepted for publication October 18, 1990.

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Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Table 1.—Athletes Aged 30 Years or Younger With Sudden Unexpected Cardiac Death*

Disease	Total No. (%)	With Exercise	Nonexercise	Exercise Unknown
Hypertrophic cardiomyopathy	20 (24)	5	1	14†
Coronary artery abnormalities	15 (18)	12	0	3
Coronary artery disease	12 (14)	9	0	3
Myocarditis	10 (12)	9	1	0
Marfan's syndrome	3 (4)	3	0	0
Dysrhythmias	2 (2)	2	0	0
Mitral valve prolapse	3 (4)	3	0	0
Other	9 (11)	4	0	5
No cause identified	10 (12)	6	3	1

*Studies reviewed for this table involved reports of athletes only (Tsung et al,⁷ Thomas and Cantwell,⁸ Maron et al,¹¹ Cantwell,⁵⁰ and James et al⁷⁶) or of athletic endeavors (Topaz and Edwards,⁹ and Lynch³⁷). "Other" category primarily included idiopathic concentric cardiac hypertrophy or acute rheumatic heart disease.

†Most of the subjects were actively exercising.

Table 2.—Signs and Symptoms Associated With Hypertrophic Cardiomyopathy

Signs and Symptoms
Symptoms
Sudden death
Dyspnea
Fatigue
Syncope
Angina
Seizures
Physical examination
Palpation
4th heart sound
Brisk carotid upstroke
Pulsus biferiens
Double apical impulse
Auscultation
Harsh left precordial ejection murmur
Murmur diminishes with squatting
Murmur increases with standing
Laboratory examination
Echocardiographic changes
Asymmetric septal hypertrophy with septal-free wall ratio >1.3
Diminished left ventricular cavity
Systolic anterior motion of the anterior leaflet of the mitral valve
Discrete (nonseptal) areas of hypertrophy
Diastolic dysfunction (impaired filling)
Cardiomegaly on chest roentgenogram
Electrocardiographic changes
Left ventricular hypertrophy
Repolarization abnormalities
Dysrhythmias

be double, a palpable fourth heart sound, pulsus biferiens,¹⁸ and a systolic murmur at the lower left sternal border to apex that diminishes on squatting and increases in intensity on assuming a standing position.²⁶ Occasionally, the highly conditioned athlete may have some findings that mimic HCM. The differentiation of this "athlete's heart" (Table 3) from HCM should be made by a cardiologist.

When the findings from a family history or physical examination are suggestive of HCM, the diagnosis is confirmed by two-dimensional and M-mode echocardiographic examination (Table 2).¹³ The electrocardiogram is not diagnostic but is usually abnormal,^{13,18,27,28} and cardiomegaly is often found on a chest roentgenogram.¹⁹ Twenty-four- and 48-hour ambulatory monitoring is ab-

normal in a very high percentage of patients²⁹ and has potential prognostic significance.²²

The athlete with HCM should be restricted from strenuous sports, dynamic or static, but may be permitted a light-exercise regimen.

CORONARY ARTERY ABNORMALITIES

Aberrant Coronary Arteries

Normal coronary artery anatomy is demonstrated in Fig 1 (top). Aberrant origin of the left coronary artery from the right sinus or the right coronary artery from the left sinus coursing between the aorta and the right ventricular outflow tract have been associated with SUD (Fig 1, center and bottom).^{4,30} Other coronary anomalies have more rarely been associated with SUD.³⁰⁻³⁷ The most frequent cause of SUD resulting from aberrant coronary origin is the left coronary artery originating at an acute angle from the right sinus of Valsalva or from the right coronary artery (Fig 1, center).³⁰ In the necropsy study by Cheitlin and colleagues,³⁰ 97% of subjects with an SUD attributed to left coronary artery aberrancy were younger than 22 years, and 78% of them died during exercise or immediately thereafter. Other authors have also found an association with an aberrant right coronary artery, exercise, and sudden death.³⁶ A tragic outcome may also result when the myocardium is supplied by a single coronary artery.³²

Symptoms of aberrant coronary arteries include those symptoms associated with myocardial ischemia, ie, anginal chest pain and especially syncope with exertion.⁶ However, as with HCM, sudden death may be, and often is, the presenting symptom, and the results of physical examination are usually entirely normal.

Any patient with syncope *during exercise* should have a cardiology consultation, and the cardiologist is obligated to address the possibility of coronary aberrancy. An aberrant left coronary artery coursing between the aorta and right ventricular outflow tract should be corrected. It is our experience that, once corrected, it may be possible to return to full athletic activity under medical supervision.

Kawasaki Disease

The authors are unaware of SUD in an athlete secondary to Kawasaki disease. However, a medical student at our institution did require coronary artery bypass surgery in adolescence as a result of Kawasaki disease as a child. Myocardial infarction and sudden death are well-recognized complications of Kawasaki disease.³⁸⁻⁴⁰ Coronary stenosis

Table 3.—Hypertrophic Cardiomyopathy vs 'Athlete's Heart'*

Echocardiographic Findings	Hypertrophic Cardiomyopathy	Athlete's Heart
Left ventricular cavity size	Diminished	Normal or increased
Septal-posterior wall thickness ratio	>1.3	<1.3
Diastolic function	Diminished left ventricular compliance and diastolic filling	Normal left ventricular compliance and filling
Evidence of inheritance (via echocardiogram)	Yes	No

*Echocardiographic signposts are listed that distinguish hypertrophic cardiomyopathy from athlete's heart, which results from intensive athletic training (see text).

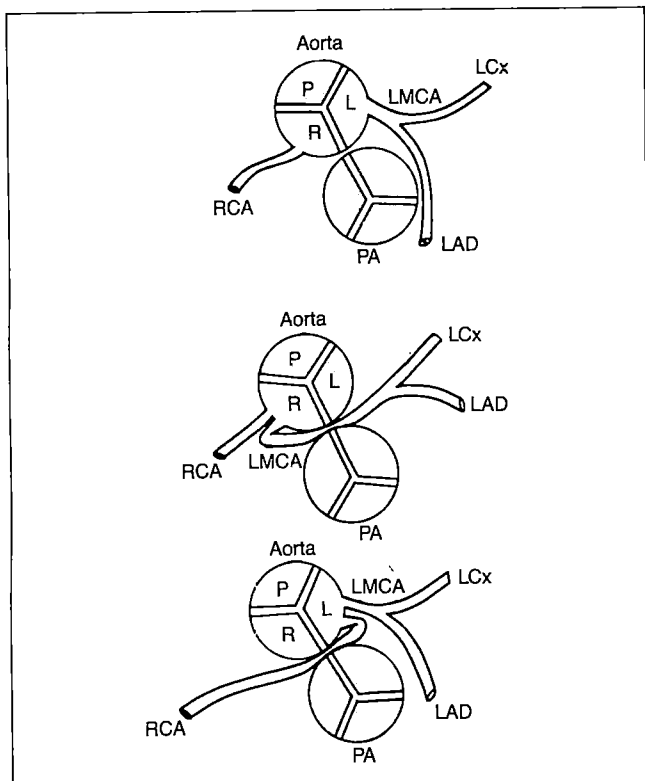


Fig 1.—Normal and aberrant coronary anatomy. Top, Normal origin and course of the coronary arteries. Center and bottom, Two most common congenital coronary artery aberrations associated with sudden unexpected cardiac death. PA indicates pulmonary artery; RCA, right coronary artery; LMCA, left main coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; and P, R, and L, posterior, right, and left aortic cusps, respectively.

may be severe and asymptomatic.⁴⁰ Approximately 25% of all myocardial infarctions in a nationwide study in Japan occurred several years after the initial disease. Although the majority of children in whom coronary artery stenosis will develop have coronary abnormalities by echocardiographic examination at the time of the initial disease, a small percentage may have a normal echocardiogram, and later, coronary artery stenosis will develop.⁴⁰

The authors would recommend that any child with a history of Kawasaki disease, who at the time of initial disease had echocardiographically documented coronary changes, prolonged fever, or congestive heart failure without subsequent documentation of normal coronary arteries, should be seen by a cardiologist before athletic participation.

ATHEROSCLEROTIC CORONARY ARTERY DISEASE

While sudden cardiac death in adults older than 35 years is almost exclusively secondary to atherosclerotic coronary

artery disease, children and young adults rarely die of coronary artery disease (Table 1).

Premature atherosclerotic coronary artery disease, resulting in a myocardial infarction or symptoms of ischemia in the second or early third decade of life, is usually the result of a severe familial dyslipidemia, most commonly severe heterozygous type II⁴¹ or homozygous type II hypercholesterolemia. The gene for this is present in one of every 500 people.⁴¹ Therefore, the statistical likelihood of the homozygous state occurring is only one per million. Nevertheless, a component of the preparticipation assessment should include a family history of premature cardiovascular death or hypercholesterolemia. A fasting lipoprotein profile should be measured on all individuals with a positive family history.

MYOCARDITIS

Active, acute myocarditis is an inflammation of the myocardium that is demonstrated on a biopsy specimen by lymphocytic infiltration of the myocardium associated with focal necrosis. Sudden cardiac death has been reported at rest and during exercise with both acute and chronic myocarditis.^{12,37,42,44,45} Noren et al observed histologic evidence of myocarditis in 17% of SUDs in children younger than 16 years, while in a similar cohort of traumatic deaths, only 2% were observed to have myocarditis.⁴² The proportion of sudden cardiac death ascribed to myocarditis has been reported to range from 18% to 29%.^{2,12,43}

Myocarditis, sudden death, and exercise, are probably secondary to conduction system inflammation.^{44,45}

Signs of myocarditis may range from only a mild but persistently elevated heart rate to ectopy, cardiomegaly, and signs of congestive heart failure. The electrocardiogram may show diffusely low voltages, ST-segment abnormalities, ventricular ectopy, fixed coupling, and/or heart block.^{43,46,47}

Without symptoms or signs suggestive of myocardial involvement, the diagnosis of myocarditis is exceedingly difficult, if not impossible, to make. To restrict participation on the basis of a low-grade fever, or to recommend evaluation of such noncardiac symptoms by a cardiologist, is both impractical and unrealistic. Many athletes "play through" a cold or mild febrile illness, especially if they are highly competitive. For the athlete who does not feel well because of a febrile illness, participation should be restricted. For the athlete who has signs or symptoms suggestive of myocardial involvement (as listed above), restriction in athletic participation and a cardiovascular evaluation are recommended.

MARFAN SYNDROME

Marfan syndrome is a constellation of physical signs that primarily involve the musculoskeletal, ocular, and cardiovascular systems as a result of connective tissue derangement. The overall incidence of Marfan syndrome in its

Table 4.—Signs and Symptoms of Marfan's Syndrome*

Signs and Symptoms
Musculoskeletal
Arachnodactyly
Pectus deformity
High narrow palate
Height >95th percentile
Hyperextensible joints
Vertebral column deformities
Pes planus
Striae distensae
Inguinal hernia
Cardiovascular
Mitral valve prolapse
Aortic root dilation
Mitral regurgitation
Aortic regurgitation
Congestive heart failure
Infective endocarditis
Aortic dissection
Ocular
Upward ectopia lentis
Myopia
Iridodonesis
Glaucoma
Retinal detachment

*Findings are listed from most common to least common from top to bottom for each section (adapted from Missri and Swett⁴⁹).

clinically diagnosable form is five to eight persons per 100 000.⁴⁸ It is inherited as an autosomal dominant with variable expression. It may occur sporadically in approximately 15% of cases.⁴⁹

There have been recent and well-publicized reports of athletes⁵⁰ dying suddenly of complications of this syndrome, and most necropsy reviews of sudden cardiac death in young athletes have included cases of Marfan syndrome (Table 1).^{1,2,12}

One or more musculoskeletal findings are seen in all patients (Table 4) although no one particular finding is found in all patients.⁴⁹ Other signs of musculoskeletal involvement, not listed in Table 4, include protrusion of the thumb across the palm when the thumb is enclosed in a fist and the overlap of the tip of the thumb and proximal interphalangeal joint of the third finger when the thumb and third finger are wrapped around the opposite wrist.

Cardiovascular findings include signs associated with mitral valve prolapse (MVP) and, less frequently, aortic insufficiency. Echocardiographic findings include up to a 100% incidence of MVP.^{50,51} There is also a high percentage of aortic root dilation⁵¹ early in the clinical course. Other echocardiographic findings are noted in Table 4.

Ocular abnormalities are found in 70% of patients,⁴⁹ with the most common finding being ectopia lentis, whereas myopia, iridodonesis, and secondary glaucoma are less common (Table 4).

As a syndrome, diagnosis is based on physical findings with supportive laboratory evidence. According to Pyeritz and McKusick,⁵² two of four major findings are necessary for diagnosis. These include: (1) a positive family history, (2) ectopia lentis, (3) aortic root dilation, and (4) either severe kyphoscoliosis or anterior thorax deformities.

If the diagnosis is suspected, a cardiologist should be consulted. We reexamine our patients every 6 to 12 months, depending on the severity and stability of the cardiac findings. If the aortic root measurements are normal, strenuous, and dynamic, but not static or isometric, sports may be performed. Other family members should be examined, and genetic counseling is mandatory.

MVP

Isolated MVP may occur with or without mitral insufficiency. It has been reported to occur in less than 1% of males and 6% of females.⁵³

Although some authors believe MVP is never associated with SUD in children,⁵⁴⁻⁵⁶ there are at least six reported cases that list MVP as the cause of death in children.^{7,57,58} In two of the six cases cited,^{9,57} there was a strong family history of sudden cardiac death at a young age with an autosomal dominant-type inheritance. Autopsies on these family members who died suddenly did not reveal MVP in the majority of cases, leading one to suspect that while a genetic predisposition to sudden death existed, it was unrelated to MVP.

Sudden death associated with MVP is usually attributed to dysrhythmias.⁵⁹⁻⁶¹ Although some studies have shown a causal relationship between MVP and exercise-induced ventricular extrasystoles,^{54,62,63} the dysrhythmias are not commonly associated with symptoms^{57,59,62,64-69} or sudden death.^{53,61}

The authors' approach to sports participation for the athlete with MVP is pragmatic. All patients with an isolated prolapse, without symptoms or signs of associated lesions or disease, and with a negative family history of SUD, are allowed full participation. Noninvasive screening tests, including echocardiography, exercise testing, and Holter monitoring, are not routinely done. For the youngster with a history of syncope (especially with exercise), palpitations, chest pain with exercise that disrupts normal activity, or a family history of sudden death, a more intensive investigation is indicated.

The athlete with MVP and associated *exercise-induced* syncope, anginal chest pain that limits full activity, or complex ventricular ectopy should be restricted from sports unless cleared by a pediatric cardiologist.⁵³

DYSRHYTHMIAS

In all the conditions previously discussed, it is believed that malignant dysrhythmias represent a final common pathway for SUD. However, there are primary disorders of automaticity, conduction, and repolarization that are, of themselves, potentially lethal without the presence of a hemodynamic abnormality. These include sinus node disturbances,^{70,71} exercise-induced ventricular ectopy,⁷²⁻⁷⁴ disorders of conduction⁷⁵⁻⁷⁷ such as in the Wolff-Parkinson-White syndrome, and repolarization abnormalities such as the long QT syndrome⁷⁸ that occurs in an autosomal dominant form, the Jervell and Lange-Nielsen syndrome, and an autosomal recessive form, the Romano-Ward syndrome.

Syncope is the most common symptom of serious rhythm disturbances,⁷⁸ and exercise may increase the likelihood of both syncope⁷⁹ and sudden death.⁶⁰

The American College of Cardiology guidelines for athletic participation⁷⁹ recommend restrictions of athletes with syncope, presyncope, or worsening arrhythmia. Patients with structural heart disease in association with sinus node dysfunction, junctional escape rhythm associated with syncope or exercise intolerance, and poorly regulated supraventricular tachycardia should also be restricted. Patients with Wolff-Parkinson-White syndrome with a family history of sudden death, documented episodes of supraventricular tachycardia, or premature ventricular complexes exacerbated by exercise are also discouraged from strenuous sports participation, especially if they are not controlled medically. Conversely, without syncope, structural heart disease, or exercise exacerbation of dysrhythmias, these rhythm disturbances do not preclude full activity. In fact, endurance athletes often demonstrate "benign" dysrhythmias, such as marked sinus

PREPARTICIPATION HEALTH EXAMINATION RECORD

(11-14)

(Office use only)

(6-8)

(7-8)

School

Grade

Last Name

First Name

Middle Initial

Age

(9-10)

(11)

Race:

Black

White

Other

Sex:

Male

Female

This application to compete in interscholastic athletics is entirely voluntary on my part and is made with the understanding that I have not violated any of the eligibility rules and regulations of the State Association.

Date

Signature of Student

Parent's or Guardian's Permission & Release

I hereby give my consent for the above named student to represent his or her school in the athletic activities except those indicated on this form by the examining physician provided that such athletic activities are approved by the State Association. I also give my consent for the student to accompany the school team on any of its local or out-of-town trips.

The Richmond County Board of Education has no responsibility to provide first aid at any of the games and the parents understand that the risk of injury is assumed by the student and parents when they are executing this form. However, in the event physicians, physical therapists, physician's assistants, nurses or other persons trained in the rendering of first aid are available, as volunteers or otherwise, and render aid to any student injured during the course of any such activities or travel, then the parents do hereby release and forever discharge such persons and the Richmond County Board of Education from any liability arising out of any first aid or immediate treatment of injuries.

Typed or Printed Name of Parent or Guardian

Signature of Parent or Guardian

Address

Phone

Date

HEALTH HISTORY

(To be completed by Student and Parents prior to examination)

(13-24)

Yes

No

Has this student had any:

1. Chronic or recurrent illness?

2. Illness lasting over one week?

3. Hospitalizations?

4. Surgery other than tonsillectomy?

5. Missing organs (eye, kidney, testicle)?

6. Allergy to any medication?

7. Problems with heart or blood pressure?

8. Chest pain with exercise?

9. Dizziness or fainting with exercise?

10. Dizziness, fainting, frequent headaches, or convulsions?

11. Concussion or unconsciousness?

12. Heat exhaustion, heat stroke, or other problems with heat?

(25-38)

Yes

No

Does this student:

13. Wear eyeglasses or contact lens?

14. Wear dental bridges, braces, plates?

15. Take any medication?

Is there any history of:

16. Injuries requiring MD treatment?

17. Neck injury?

18. Knee injury?

19. Knee surgery?

20. Ankle injury?

21. Other serious joint injury?

22. Broken bones (fractures)?

23. Is there any reason why this student should not participate in sports?

24. Has any family member died suddenly at less than 40 years of age of causes other than an accident?

Date of last known Tetanus (lock jaw) shot:

Use this space to explain any of the above numbered YES answers or to provide any additional information:

PHYSICAL EXAMINATION

Card two (1-4)

(Office use only)

Date

Height

Weight

Pulse rate

Blood pressure

Vision: Right

Left

Normal 1

Abnormal 2

Abnormal 3

Abnormal 4

(51-70)

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

Neurological

Comments

Examiner

Problem Code (1-47)

1. Eyes

2. Ears, Nose, Throat

3. Mouth and Teeth

4. Neck (soft tissue)

5. Cardiovascular

6. Chest and Lungs

7. Abdomen

8. Genitalia-Hernia

9. Sexual Maturity

10. Skin and Lymphatics

11. Neck

12. Spine

13. Shoulders

14. Arms and Hands

15. Hips

16. Thighs

17. Knees

18. Ankles

19. Feet

20. Neurological

Based on this history and physical exam, the following abnormalities were found and may need treatment:

1.

2.

3.

(71)

PARTICIPATION RECOMMENDATIONS

1. There were no history or physical findings on this exam which would prohibit this student from participating in competitive athletics.

2. This student should have the following health problems evaluated or treated prior to participating in competitive athletics.

3. This student has health problems which would prohibit him or her from participating in competitive athletics.

PHYSICIAN

Fig 2.— Left and right, Preparticipation screening forms. These forms (devised by the Richmond County, Georgia, Medical Society and adopted by the American Academy of Pediatrics, Elk Grove Village, Ill) are recommended for pre-sports participation screening of young athletes (used with permission of the American Academy of Pediatrics⁸⁶).

bradycardia and type I second-degree atrioventricular block as a result of conditioning.⁶³ In general, supraventricular and ventricular premature beats are not worrisome if they are unifocal and if they abolish or diminish with exercise. Even ventricular couplets appear to be benign in the context of an otherwise normal heart.⁸⁰ First-degree and second-degree Mobitz type 1 heart blocks without syncope, structural heart disease, or exacerbation with exercise need no restriction. Because there is variability in approach to these rhythm disturbances, a cardiologist familiar with children and sports should be consulted before such a youngster is allowed to participate.

ADDITIONAL ISSUES

Almost all children who die suddenly with aortic stenosis have severe disease.^{2,81-83} The probability of a child with severe aortic stenosis slipping through a well-conducted sports physical examination undetected is highly unlikely. In a series that reported sudden death, virtually all patients were symptomatic before their final episode.⁸¹⁻⁸³ However, as the severity of the aortic stenosis can sometimes not be accurately gauged by noninvasive testing, youngsters with aortic stenosis should be examined by their pediatric cardiologist.⁸⁴ Those children with severe or symptomatic aortic stenosis should never participate in sports unless their obstruction is relieved.

Hank Gathers' death has raised the issue of having a courtside defibrillator for those athletes at risk for ventricular fibrillation. While not unheard of, to have a defibrillator and personnel trained in its use present at all games and practices cannot be routinely justified except

under extraordinary and clearly understood conditions. All parties must be aware that the athlete has a potentially lethal condition. The legal and financial implications and responsibilities must be developed on a case-by-case basis.

PREVENTION

In the Epstein and colleagues⁵ report of sudden cardiac death in young, highly competitive athletes, only 25% had signs and symptoms suggestive of a cardiac abnormality, and of those with such signs and symptoms, most of the athletes were misdiagnosed. Other authors suggest that for the more common lesions already discussed, the potential of diagnosing these patients' conditions by history and physical examination alone ranges from 0% to 25%. The authors of this review do not accept this pessimistic outlook. They believe that with a competent screening history and physical examination, as recommended by the American Academy of Pediatrics (Fig 2), most patients with a significant cardiac lesion can and should be identified and referred for accurate diagnosis and management.

Unfortunately, this screening process has not been uniformly adopted, and many states do not require more than a physician's signature on a preparticipation form.⁸⁵

SCREENING

An ideal screening evaluation should be based solely on history and physical examination results. It should require a modest amount of equipment and time. It should only be performed in a reasonably quiet environment and never in the locker-room atmosphere. Locker-room evaluations are perfunctory and potentially dangerous because they may provide a false sense of security.

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The history can most efficiently be taken via a preparticipation questionnaire, such as the one used in the Richmond County, Georgia, school system⁸⁶ and recommended by the American Academy of Pediatrics Committee on Practice (Fig 2). Syncope (question 9) is often the most common symptom before death⁸⁷ and should prompt referral to a cardiologist for a thorough evaluation. A positive family history of sudden unsuspected cardiac death is also important (question 24). It is well known that seizures may be the initial and only manifestation of the prolonged QT syndrome,⁸⁸ and prolongation of the corrected QT interval should be looked for in any child with a history of seizures. The physical examination, like the history, should be complete but need not be extensive. The examination is based on the traditional methods of inspection, palpation, and auscultation⁶ and, of course, should always include carefully measured vital signs. The authors have previously discussed the absolute impracticality of the echocardiogram as a screening method for SUD.⁶ The electrocardiogram costs much less as a screening tool but, in the authors' opinion, is equally impractical, insensitive, and even less specific.

THE YOUNG ATHLETE AT KNOWN INCREASED RISK

What are the responsibilities toward the young athlete (and his or her family) who is identified as having a potentially lethal defect? Whose responsibility is it to provide emergency treatment if the athlete is allowed continued participation?

The authors believe it is the primary responsibility of the athlete and his or her parents to comprehend the cardiac lesion involved and the limitations required. Obviously, the consulting cardiologist and referring physician must work closely with the family and team and league officials to ensure that all vital information is accurately and clearly communicated. It seems reasonable to the authors to recommend that all coaches be trained in basic cardiopulmonary resuscitation and first aid.

CONCLUSIONS

Sudden unexpected death in otherwise healthy children and adolescent athletes is a source of concern and anxiety for physicians, parents, and coaches. However, the concern is out of proportion to the scope of the problem. The cardiac lesions that may result in sudden cardiac death include hypertrophic cardiomyopathy, coronary artery anomalies, Marfan syndrome, and primary arrhythmias. A concise, directed screening history and physical examination should identify the majority of the athletes with these lesions.

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Tattooing Behavior in Adolescence

A Comparison Study

James A. Farrow, MD; Richard H. Schwartz, MD; Joop Vanderleeuw, MD

• We characterize associations with and motivations for tattooing in adolescents through data from a controlled, three-group comparison of adolescents from a substance abuse treatment program, detention center, and private pediatric practice. We surveyed 474 adolescents (12 to 18 years old) with tattoos (12%) and without tattoos (88%). The private pediatric practice was the control site. A 34-item questionnaire was used to profile the three groups and their primary associations with tattooing with respect to race, drug use, school attendance, school grades, parental marital status, family income, tattooing by family members, criminal activity, and involvement with satanic rituals. Tattooing was significantly ($P < .005$) associated with all of these variables in the ways described, as was knowledge of its association with human immunodeficiency virus infection. No interventions were made. Tattooing is common in adolescents and is associated with low self-esteem, delinquency, drug abuse, family and peer modeling, and participation in satanic rituals. Addressing the behavior as a health problem is discussed.

(AJDC. 1991;145:184-187)

Tattooing is common among some adolescents. Whether the tattooing is of the more common, amateur variety, or scribed by a professional tattoo artist, the motivations for such behavior and its health implications for adolescents have not been clearly delineated. Tattooing has many potential medical complications.¹ Tattooing is practiced by adolescents in solitude, among peers, and, occasionally, as part of rituals.²⁻⁴ In some instances, tattooing is deliberate self-harm akin to the "carving" behaviors seen in suicidal and depressed adolescents.^{5,6} Most tattooing during adolescence is not, however, indicative of psychosis or self-destructive tendencies.⁷ As with carving, adolescents may use tattooing as a way of displaying affection for a boyfriend, girlfriend, or popular rock music group.⁵ The purpose of this three-group comparison study was to better characterize and delineate the motivation for tattooing among adolescents, a subject that is often misunderstood or misinterpreted by pediatricians.

Accepted for publication September 4, 1990.

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SUBJECTS AND METHODS

A convenience sample of 474 adolescents with a mean age of 15.9 years (range, 14.9 to 17.1 years) responded to a 34-item questionnaire. Respondents included 160 adolescents (71% male) in a residential drug and alcohol treatment program in suburban Washington, DC, 102 juvenile detainees (80% male) in the King County (Washington) Juvenile Detention Center in Seattle, and 212 control subjects (43% male) from a private pediatric practice in a middle-class community in suburban Virginia. Questionnaires were administered to the cohort undergoing treatment for chemical dependency and the control subjects with explicit parental consent, and to the population of detainees with a letter of explanation to the child's parent or guardian. The questionnaire was pilot-tested for understandability and readability. Areas covered by the survey included sex, race, parents' marital status, family education and income, highest school year completed, grade point average (GPA), school attendance/dropout status, criminal behavior, drug use, participation in satanic rituals, and tattooing behavior by family, friends, and boyfriends or girlfriends. Tattooing-behavior questions included age at first tattoo, use of a professional tattoo artist, mental state during tattooing, identification of tattoos with satanic symbolism (Fig 1), and knowledge of the relationship between acquired immunodeficiency syndrome and needle use.

Characteristics of the subject populations were analyzed using standard statistical methods. Statistical methods employed in the data analysis consisted of analyses of variance for the continuous measures and χ^2 analyses for the evaluation of differences of frequencies between groups. Means were derived using Student's *t* test.

RESULTS

Table 1 profiles subjects by study groups and summarizes subject profiles with respect to race, parental marital status and education, subject's GPA, drug use, involvement in satanic rituals, and tattooing. Among all respondents, the parents of 172 (36%) were divorced or separated, with detainees having the highest incidence of this (64 subjects, 63% of all juvenile detainees). Ninety-six subjects (60%) from the drug abuse treatment program and 100 detainees (98% of all detainees) had been arrested. Drug use was highest overall among subjects in the drug treatment program.

Of all respondents, 54 (11.4%) had some experience with satanic rituals. Adolescents from the drug treatment program were more involved in this activity than adolescents from the other two groups. Fifty-eight (12.2% of all subjects) had tattoos or had engaged in tattooing behaviors. These behaviors consisted of intentional inscription of letters or symbols with and without indelible substances. Data describing tattooing among peers and family members are presented in Table 1.



Fig 1.—A symbol inscribed by a professional.



Fig 2.—A self- or peer-inscribed tattoo.

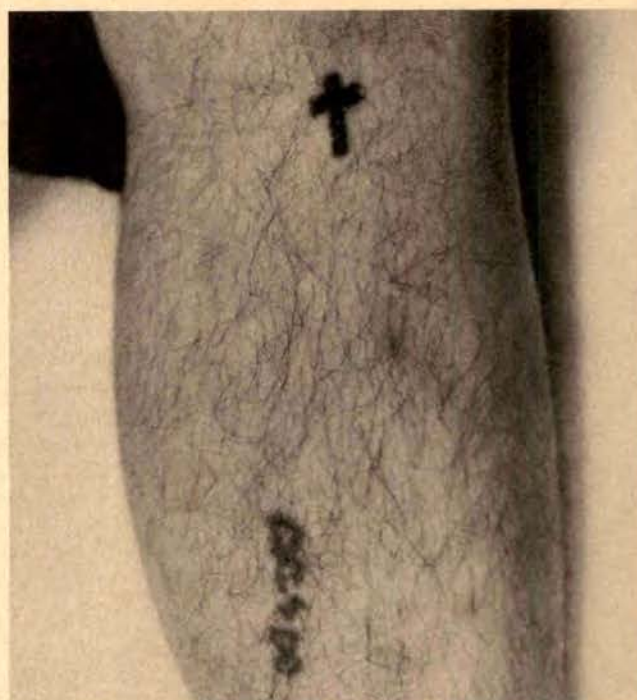


Fig 3.—A self- or peer-inscribed tattoo.

Table 1.—Subject Profiles by Study Group (N=474)*

	Drug Abuse Group (n=160)	Juvenile Detention Group (n=102)	Control Group (n=212)
Race, No. (%)			
White	143 (89)	38 (37)	198 (93)
Black	16 (10)	42 (41)	8 (4)
Hispanic	0	4 (4)	3 (1)
Asian	0	1 (1)	2 (0.9)
Other	1 (.6)	17 (17)	1 (.5)
Family history, No. (%)			
Parents divorced or separated	65 (41)	64 (63)	43 (20)
Father a college graduate	57 (36)	13 (13)	68 (32)
Family income more than \$40 000 per year	9 (6)	32 (31)	84 (40)
Family member has a tattoo	26 (16)	30 (29)	13 (6)
Mean grade point average	2.5/4.0	2.0/4.0	3.0/4.0
Subject history, No. (%)			
Arrested	96 (60)	100 (98)	7 (3)
Participated in satanic rituals	41 (26)	12 (12)	1 (0.5)
Used marijuana weekly	135 (84)	56 (55)	11 (5)
Ever used phencyclidine	84 (53)	1 (1)	7 (3)
Drunk more than 10 times	DNA	10 (10)	10 (5)
Best friend has a tattoo	36 (23)	54 (53)	4 (2)
Girlfriend or boyfriend has a tattoo	29 (18)	22 (22)	5 (2)
Subject has a tattoo	21 (13)	34 (33)	3 (1)

*In descriptions of race, percentages may not total 100 because of rounding. DNA indicates data not available.

Eight (14%) of the 58 subjects with tattoos had more than one tattoo. The ages at which their first tattoos were engraved were fairly evenly distributed through age groups. Only 10 (17%) of the 58 had had the tattoos applied by a

professional (Fig 1); the remainder were self- or peer-inscribed (Figs 2 and 3). Most tattoos were on the arms (42); other locations of tattoos included the face (two), hands (13), legs (three), chest (five), and back (one). A satanic symbol was identified on one subject (not shown). Eleven subjects (19%) were intoxicated when their tattoos were applied. Only six (10%) wanted the tattoo removed when surveyed. Seven (12%) of the tattooed adolescents had shared needles when the tattoo was created.

Table 2 profiles subjects with tattoos and notes differences between them and subjects without tattoos. Differences with respect to race, parental marital status, GPA, school attendance, arrest history, drug use, and tattooing by peers and family members were significant. Tattooing behavior was greater in children of fathers who had not graduated from college.

Most tattooed adolescents (50 subjects, 86%) came from middle-income families. Academic achievement was lower in the group with tattoos (mean GPA, 2.2 on a 4.0

Table 2.—Summary of Significant Associations With Tattooing in Adolescents*

	Group With Tattoos, No. (%) (n = 58)	Group Without Tattoos, No. (%) (n = 416)	χ^2	df
Male/female	46 (79)/12 (21)	237 (57)/179 (43)	9.3	1
Race	17.5	5
White	38 (66)	338 (81)
Black	10 (17)	54 (13)
Family history				
Parents divorced or separated	32 (55)	139 (33)	18.4	4
Father a college graduate	10 (17)	128 (31)	19.5	5
Family member has a tattoo	25 (43)	85 (20)	60.5	15
Subject history				
School dropout	25 (43)	72 (17)	19.7	1
Arrested	41 (71)	85 (20)	21.8	1
Used marijuana weekly	37 (64)	163 (39)	120.6	2
Ever used phencyclidine	12 (21)	49 (12)	8.5	1
Ever used lysergic acid diethylamide	33 (57)	136 (33)	19.5	4
Drunk more than 10 times	25 (43)	63 (15)	108.5	4
Received treatment for drug use	33 (57)	141 (34)	9.7	1
Participated in satanic rituals	15 (26)	38 (9)	14.2	1
Best friend has a tattoo	41 (71)	52 (13)	102.5	1
Girlfriend or boyfriend has a tattoo	23 (40)	32 (8)	48.4	1

**P* values were significant ($P < .005$) for all associations. The group with tattoos had a mean grade point average of 2.2 on a 4.0 scale, and the group without tattoos had a mean grade point average of 3.0 on the same scale.

scale) than in the group without tattoos (mean GPA, 3.0 on a 4.0 scale, $P = .002$). Twenty-five (43%) of the 58 tattooed subjects had dropped out of school. With respect to school attendance, only one of the control subjects had dropped out of school, while 48 (47%) of the juvenile detainees had quit school. Of the 58 subjects with tattoos, 41 (71%) had arrest records. The relationship between types of offense and having a tattoo was nonsignificant.

Most drug and alcohol use was significantly related to having a tattoo, although a selection bias is inherent in the study population for adolescents who abuse drugs. A history of having received treatment for drug use was likewise associated with tattooing ($P = .002$). Fifteen (26%) of the tattooed adolescents had been involved in satanic rituals. Tattooing behavior was significantly associated with a best friend, girlfriend, boyfriend, or family member having a tattoo ($P < .001$).

No significant differences were evident between the responses of males and females with tattoos, although the male-female ratio was greater in the group with tattoos than in the group without tattoos. No significant difference existed among comparison groups with respect to knowing the relationship between human immunodeficiency virus (HIV) infection and tattooing. The correct relationship was acknowledged most often by the group of detainees (136 subjects, 85%). Of all subjects, 300 (63%) indicated that they knew HIV infection was related to tattooing. Eight tattooed subjects (14%) were unaware of the association. No significant difference was shown between groups with tattoos and groups without tattoos with respect to knowledge about the relationship between tattoos, needles, and acquired immunodeficiency syndrome.

COMMENT

This study reaffirms reports that tattooing is a common practice among adolescents^{5,8-10} and attempts to characterize which adolescents are most likely to engage in this

behavior. It does not define psychopathology in the study population. While many adolescents who engage in self-destructive behavior such as carving or tattooing suffer from significant psychiatric dysfunction, many also engage in the behavior because of low self-esteem or peer and family modeling and as an immediate reaction to drug and alcohol disinhibition.^{3,5-7,11,12} Further, adolescents with tattoos appear to have also experienced family dysfunction, poor academic performance, poor school attendance, delinquent or gang-related behavior, heavier drug and alcohol use, and sometimes drug dealing.

Some of these associations have been noted previously.^{6,7,12-14} To some extent, these youth are more alienated from family, school, and social institutions than their peers without tattoos. They are significantly more likely to be involved in satanic rituals. To what degree participation in satanic rituals promoted tattooing is unknown, and this study does not answer that question. Among our study population, tattooing appears to occur more from impulse than as part of any ritualistic activity.

Black adolescents were slightly more likely to have a tattoo than the general study population, with the highest proportion of black subjects coming from the detention population (42 subjects, 41%; Table 1).

All three groups appeared to be knowledgeable about the association between HIV infection and the use of needles for tattooing.¹⁵ However, a large minority (175 subjects, 37%) of the total population was not aware of the potential for transmitting HIV infection through contaminated tattooing apparatus.¹⁶ Adolescents with tattoos were not significantly less knowledgeable about this risk than those without tattoos. In general, our results indicate the need for more education of all adolescents about the relationship between HIV infection and tattooing.

Our findings have implications for how tattooing of adolescents is viewed in the clinical setting. Clinicians with

tattooed adolescent patients should use these findings as a stimulus for discussions about self-care and disease prevention. Although tattooing is most often associated with underlying family modeling, low self-esteem, an impulsive personality style, and deviant behaviors, it should be addressed outright as a health issue. Physicians should also recognize that some tattoos symbolize involvement in satanic activities or indicate a state of depression and self-destructive tendencies. They should follow up on the behavior by investigating these possibilities. This study also confirms an association between tattooing and drug abuse. Tattooing, therefore, can be seen as another indicator of the deleterious nature of chemical dependency in this age group. All clinicians should be aware of the potential significance and underlying motivations of tattooing in adolescence and discuss the behavior while providing guidance to young patients.

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Skateboarding Injuries in Children

A Second Wave

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• Motivated by a number of skateboard-related injuries seen in an emergency department, we undertook an investigation of skateboarding injuries in the mid-1980s. We studied US Consumer Product Safety Commission injury frequency estimates, which indicated a resurgence of these injuries: 19 182 in 1984 and 37 180 in 1985. Children 10 to 14 years old were injured with greatest frequency. Nontrivial injuries were more common among children younger than 5 years old, reflecting a larger proportion of head and neck injuries. Boys sustained more frequent and more severe skateboard-related injuries. Observed injury patterns (head and neck injuries in younger children, extremity injuries in older children, and more severe head and neck injuries in older children) probably reflect the role of psychomotor development on both risk exposure and biomechanics. Likely prevention strategies include warnings against skateboard use by children younger than 5 years, prohibition of skateboards on streets and highways, and the promotion of use of helmets and other protective gear.

(AJDC. 1991;145:188-193)

Skateboarding is a visible activity of modern childhood whose popularity has waxed and waned since skateboards were first marketed in the 1960s. It provides pleasure and entertainment, yet also is a source of injury. The number of injuries related to skateboards peaked in 1977 and then declined through the early 1980s. During the several subsequent years, we noticed a rising number of skateboard injuries in the Children's Memorial Hospital emergency department, Chicago, Ill. Review of the US Consumer Product Safety Commission (CPSC) data indicated that such injuries were again rising in incidence nationally. We undertook an investigation of skateboard injuries in the 1980s with the following objectives: (1) to characterize the 1980s outbreak, (2) to compare certain aspects of this outbreak with that which occurred in the 1970s, and (3) to identify preventable causes of contemporary skateboarding injuries.

Accepted for publication August 6, 1990.

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Read before the Annual Meeting of the Midwest Society for Pediatric Research, Chicago, Ill, November 11, 1987, and the National Meeting of the American Public Health Association, Boston, Mass, November 14, 1988.

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MATERIALS AND METHODS

Data were obtained from the CPSC Injury Information Clearinghouse in Washington, DC, concerning injuries associated with skateboard use (CPSC code 1333) during 1976 and 1977 (the peak years of the last outbreak) and 1984 and 1985 (the two most recent years about which complete data were available at the time of data collection). The data reviewed included the following:

(1) Age and sex-specific injury frequency estimates were obtained from the National Electronic Injury Surveillance System (NEISS) database. The NEISS estimates are derived from surveillance of statistically representative emergency departments in the United States (119 in 1976 and 1977; 73 in 1984; and 64 in 1985). These data consist of age- and sex-specific injury information, including body part injured, disposition, location, and severity. The CPSC severity coding scheme was developed by a panel of authorities (epidemiologists and other physicians) during the 1970s. Injuries were assigned severity ratings based on subjective opinions of the panel of authorities (Bart McDonald, CPSC spokesman, oral communication, 1989). The frequency estimate data reviewed included a brief description of each skateboard injury reported during the period studied. Injury frequency estimates are derived from NEISS reports using weightings for each recorded visit, based on the representativeness of the emergency department in which it originated. (2) Summaries of cases were reported to the CPSC by news clippings, consumers' complaints, the medical examiners' and coroners' alert program, government agency referral, and other sources during the years studied. (3) Brief reports of in-depth investigations were gathered by the CPSC staff of selected injury cases from 1977 through 1979 and 1983 through 1985. (4) Information on deaths from 1984 through 1987 was compiled by the CPSC from state health department death certificates. (5) Finally, CPSC product summary reports (on hundreds of products) were collected for 1976 through 1986.

Until 1979, 119 hospitals gathered NEISS data. In 1980, 11 large hospitals were added but, owing to financial constraints, the total number of reporting hospitals was reduced later that same year to 74 (nine of the 11 large hospitals remained). The estimated sampling error increased only slightly over what it was in the 1970s, ie, prior to the addition of the large hospitals. A further reduction in the number of reporting hospitals occurred in 1984 (reducing the total to 65); again the sampling error was estimated to have increased only slightly because the reductions affected mainly smaller hospitals (which were effectively substituted for by larger hospitals) (Bart McDonald, CPSC spokesman, oral communication, 1989).

To permit calculations of age-specific injury incidence rate estimates, data were obtained on age-specific population counts from the 1980 US census and on population projections for 1976, 1977, 1984, and 1985.¹ Information about skateboard manufacturing regulations, industry safety standards, and protective gear was obtained by personal communication with the CPSC, skate-

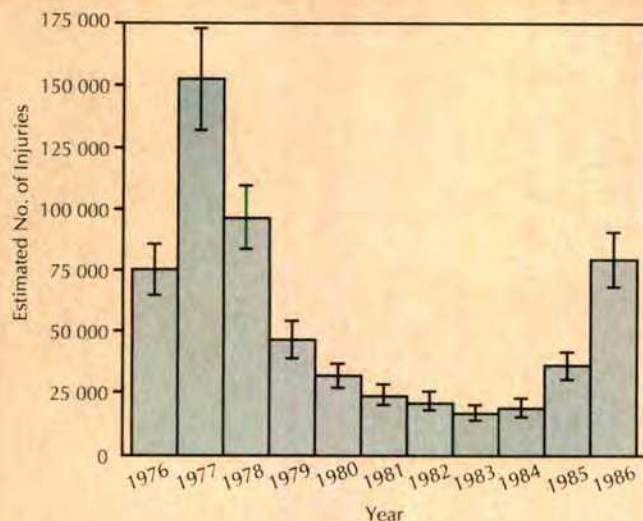


Fig 1.—The number of injuries.

board manufacturers, manufacturers of protective gear for skateboarding, and skateboard competition promotional organizations (oral communication with spokespersons from the Powell Corp, Santa Barbara, Calif, and the Pro Tech Corp, Bellevue, Wash, which are manufacturers of skateboard equipment, and from the National Skateboard Association, San Bernardino, Calif, 1988).

Data were analyzed on a computer (IBM System 38). The strength of bivariate relationships between categorical variables was evaluated using the χ^2 statistic, with the level of significance set at P being less than .01.

RESULTS

The Current Outbreak

Number of Injuries.—More than 150 000 skateboard-related injuries occurred in the peak year of 1977, after which the incidence declined through 1983 (16 836). It then began to rise again (Fig 1): 19 182 injuries were reported in 1984 and 37 180 injuries were reported in 1985. Data concerning 1986, released after the data reported herein had been analyzed, showed an incidence of 81 000—a 120% increase from the year before.

Demographic Analysis.—Of all skateboard related injuries in the 1980s, 88% occurred to persons younger than 20 years, and 83% occurred among boys (range, 65% in boys 5 years old to 100% in boys younger than 1 year). For most analyses, we grouped data according to standard age groupings and labeled these groups as follows: 0 to 4 year olds, infants and toddlers; 5 to 9 year olds, young children; 10 to 14 year olds, young adolescents; and 15 to 19 year olds, older adolescents. Table 1 compares the estimated number of injuries by age group in the 1970s and the 1980s. A greater proportion of children 9 years old or younger were injured in the 1980s ($P < .001$). The largest number of injuries occurred among young adolescents. This age group, which represents 24% of the pediatric population and 6.5% of the total population, accounted for 45% of all injuries in the 1980s. The standard groupings obscure the fact that the incidence of injury and sex distribution for 15-year-old children seem to follow patterns for 10 to 14 year olds more closely than for 16 to 19 year olds, as seen in Fig 2, which displays incidence by year of age.

Body Part Injured.—Reported injuries were grouped into three anatomic regions: head and neck, extremities, and trunk. Almost 75% of all injuries involved the extremities. Greater than 90% of all injuries involved either the extremities or the head and neck.

There was a strong interaction between age and injured body part (Fig 3). With each increasing age group, the pro-

Table 1.—Injury Frequency by Age Grouping, 1970s and 1980s, Estimated Number of Injuries

Age, y	1976-1977, No. (%)	1984-1985, No. (%)
0-4	3272 (1.5)	2384 (4.2)
5-9	33 654 (14.9)	10 386 (18.4)
10-14	120 054 (53.3)	25 402 (45.1)
15-19	40 739 (18.1)	11 582 (20.5)
>20	27 679 (12.3)	6608 (11.7)

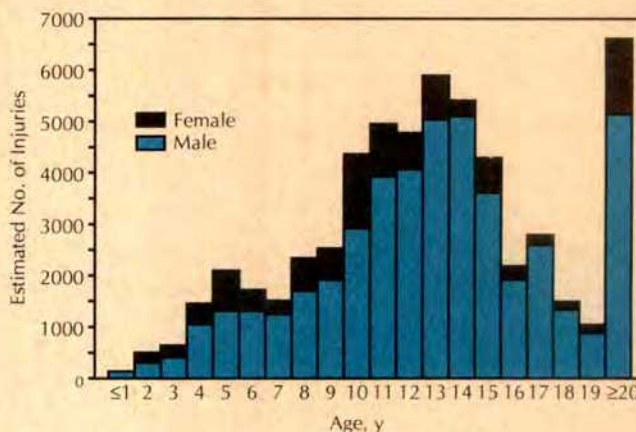


Fig 2.—The incidence of injury and sex distribution.

portion of head injuries decreased while the proportion of extremity injuries increased ($P < .001$).

Severity of Injury.—Six levels of severity (1=low to 6=high) were coded by the CPSC (Table 2). We collapsed these to create three categories of severity: mild (1 to 2), moderate (3 to 4), and severe (5 to 6). Moderate injuries were the most frequent in every age group younger than 20 years, and most head injuries in all age groups were classified as moderate. No extremity injuries were scored as severe.

Severity and Age.—Overall, the proportion of mild injuries increased with increasing age (Fig 4). However, the proportion of mild head and neck injuries decreased with increasing age group (Fig 5) ($P < .001$), with the proportion of head injuries that were severe being largest (almost 23%) among young adolescents. The distribution of mild and moderate extremity injuries was nearly constant across age groups.

Location of Injury.—We collapsed the nine different injury occurrence location codes used by NEISS to form three groupings: home (home, apartment, condominium, farm), streets and highways (streets and highways), and other public places (school, industrial, and sports or recreational places). Almost 80% of all injuries occurred either at or near the home (49%) or on streets and highways (30%).

Location and Age.—Among infants and toddlers, 15% were injured on streets and highways compared with 23% for young children and more than 30% for adolescents ($P < .001$).

Injury Circumstances.—In-depth investigation of 218 skateboard injuries revealed information about injury circumstances. Although a large proportion of these investigations reported a nonspecific cause of injury (such as "fell from skateboard" or "lost control"), several recurrent scenarios were found in the 102 cases (47%) with more information. The most common specific circumstance was

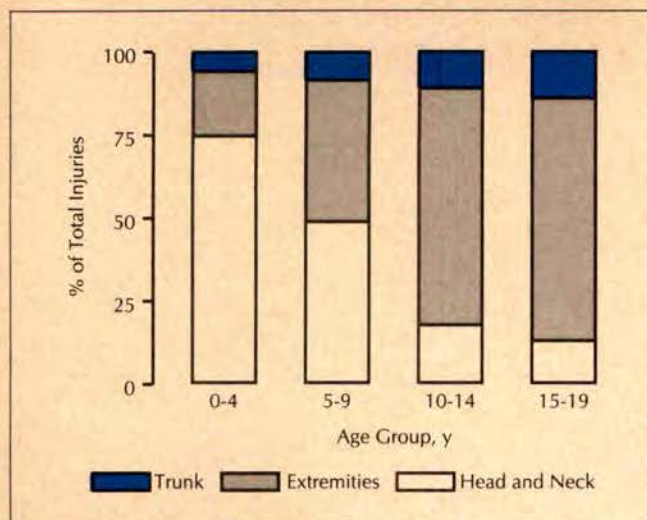


Fig 3.—The interaction between age and injured body part.

Severity	Examples
1	Sprained foot (mild injuries to small areas)
2	Contusion to lower trunk; dislocated arm, hand; puncture
3	Arm fracture; sprained neck
4	Finger crushing; head laceration; punctured eye
5	Concussion; fractured neck
6	Amputation; anoxia; arm crushing

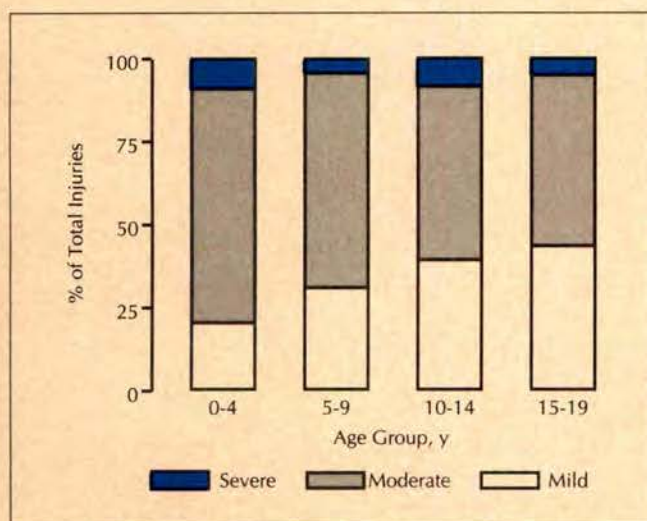


Fig 4.—The proportion of mild injuries increased with increasing age.

reported in 37 cases (17%): a moving skateboard hit an obstacle that caused a sudden cessation of the skateboard's forward motion, resulting in the rider's falling forward and off the skateboard. The obstacles encountered included sticks, stones, cracks, and bumps on the riding surface. Motor vehicles were involved in six injuries (3%) and bicycles were involved in another five injuries (2%). Nine injuries (4%) were attributed to skateboard failure.

Case reports concerning infants in the 0- to 2-year-old age range revealed additional circumstances of injury, including tripping over a stationary skateboard at home and being pushed off a skateboard by an older sibling (some-

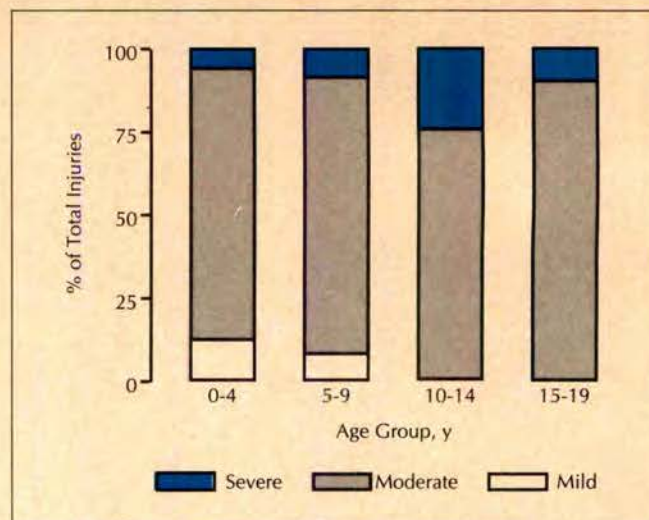


Fig 5.—The proportion of mild head and neck injuries decreased with increasing age.

times after having been placed on the board by the sibling). Most reports for children 3 to 4 years old indicated circumstances similar to those for school-age children (eg, skateboard wheel hits a small object). An additional factor in this age group may be poorer balance, as suggested by case reports of falling backwards off the board for no apparent reason.

Deaths.—According to the Reported Incident File of the CPSC, there were 36 deaths associated with skateboard use from June 1984 through August 1987. Of these, 21 (58%) involved motor vehicles. Severe head injury was the cause of death for all patients whose cause of death was reported, but the cause of death was reported in only 20% of the cases. Data from 1976 through 1979 indicate that of the 29 skateboard-related deaths reported, 90% were associated with severe head injury.

Age and Deaths.—Of the 36 deaths reported that were studied, 16 (44%) occurred in younger adolescents and 15 (42%) occurred in older adolescents. In addition, the deaths included one toddler, one young child, and three persons 20 years or older.

Changes From Past Outbreak.—Most of the patterns of injury found in the 1980s were similar to those in the 1970s. There were, however, some notable changes (Table 3). The proportion of boys among all injured children was higher. Younger children experienced a greater proportion of skateboard injuries. Hospitalization rates diminished. Finally, fewer injuries occurred at home in the 1980s, and more injuries occurred in the streets and on the highways.

Skateboard Safety Practices

The following information about skateboard safety was obtained in 1988 through oral communication with spokespersons from the Powell Corp, the Pro Tech Corp, and the National Skateboard Association. There are no skateboard manufacturing regulations, but US manufacturers report that they have set self-imposed industry standards to guard the market against lower-quality imported products. Many manufacturers produce or distribute protective gear, such as helmets, clothing, and pads, specifically designed for skateboarding. The proportion of skateboarders using protective equipment depends on the type of skateboarding practiced. Those engaged in vertical skating, such as skating on steep ramps, reportedly use protective gear most often. Vertical skating competition

Table 3.—Changes From Past Outbreak*

	1970s, No. (%)	1980s, No. (%)
Male subjects	159 378 (71)	46 160 (83)
Children younger than 10 y	36 926 (16)	12 689 (23)
Hospitalization rate	9155 (4)	1416 (2.5)
Injuries in streets and highways	15 243 (13)	15 357 (30)
Injuries occurring at home	86 878 (72)	24 162 (48)

*All $P < .001$ by χ^2 .

events reportedly require skaters to wear helmets and knee and elbow pads. Freestyle skaters wear protective gear 50% to 70% of the time, depending on the spokesperson questioned. Street skaters, who are the most numerous, wear protective gear least often.

COMMENT

In the mid-1980s, skateboards were once again associated with a large number of injuries, some fatal. The available information, based on NEISS data, indicates that of the tens of thousands of children injured annually, most were preadolescent boys.

Because the number of hospitals surveyed by NEISS decreased during the years studied, confidence in the representativeness of the demographic composition of the sample from the 1980s may be decreased as compared with that of the 1970s. However, injury patterns in NEISS data from each period are still known to be valid for other types of injuries (eg, all terrain vehicles, L. Robertson, oral communication, 1988). As the best information available, the NEISS data remain instructive regarding the relationships between maturational levels and patterns of injury. However accurate they may be as estimates of emergency department visits, the NEISS estimates are underestimates of total injury frequency, because not all injured children are brought to emergency departments. In light of this, the estimated number of injuries is all the more striking.

Injury and Development

Age and injury were related in a discernible pattern. Younger children tended to sustain more severe injuries and more head injuries. In fact, these two observations are related because the CPSC tended to rank head injuries as more severe than extremity injuries. Overall, injuries to adolescents were milder, and they included more extremity injuries and fewer head injuries than those to younger children. However, when adolescents did sustain head injuries, they tended to be more severe. Finally, adolescents were more commonly injured on streets and highways than were younger children.

Several behavioral and developmental hypotheses concerning the mechanisms of skateboard injuries emerge from the data (Table 4). Because of immature motor coordination, young children may be unable to break falls with their arms. Their disproportionately large heads (as compared with adolescents) makes their heads the leading body part in falls from skateboards. These factors combine to cause young children to have more head injuries as compared with older children. However, because most injuries in young children probably occur at low speeds while using skateboards at home, the head injuries sustained are generally not severe. As children grow older, they develop increasing motor coordination and become better able to break falls with outstretched arms, thereby preferentially injuring extremities. However, older children also tend to

Table 4.—Psychomotor Development and Injury Characteristics

Age, y	Developmental Characteristics	Exposure	Injuries
0-4	High center of gravity; poor motor coordination; light weight; inexperienced riders	Low speed; home	Head > extremities Head: mild-moderate
5-9	Lower center of gravity; fair motor coordination; heavier weight; some risk taking	Higher speed; streets	Extremities = head Head: moderate
10-19	Lowest center of gravity; good motor coordination; heaviest weight; much risk taking; experienced riders	Highest speed; streets and highways	Extremities > head Head: moderate-severe

engage in increasingly risky behavior, often away from home. Consequently, they sustain more injuries on streets and highways where high-speed injuries are more prevalent. When head injuries occur under these circumstances, they are apt to be more severe.

Product Factors

Several product factors contribute to the danger associated with skateboarding today. Skateboards have small wheels as compared with bicycles, tricycles, and other children's vehicles. These small wheels are easily affected by small interruptions in the riding surface, such as sticks, stones, and cracks. The fact that these commonly cause skateboard mishaps has previously been recognized.²⁻⁴ In addition, current construction uses urethane wheels and low rotational friction of the axles, enabling skateboards to achieve speeds of greater than 64 to 80 km/h (40 to 50 mph).⁵⁻⁷ Skateboards are designed for high maneuverability at the expense of balance and control. Slight shifts in the rider's center of gravity cause great directional changes in the skateboard's motion, necessitating considerable skill for successful operators. This, coupled with the high speed of travel and the sensitivity of the wheels to irregularities in the riding surface, contributes to skateboard hazard.

Injury Prevention

The findings reported concerning age-related skateboard injury patterns suggest several strategies for injury prevention. Children younger than 5 years lack the motor coordination and judgment to operate skateboards safely. Use by children in this age group results in severe injury and, therefore, should be vigorously discouraged.

The most serious injuries, including deaths, involve severe head injury. Therefore, protective headgear should be used at all times, as recommended by various investigators.^{2,4,7-11} Most injuries occurring to older children involve the extremities. Appropriately designed padding should prevent at least some soft-tissue injuries. The

portions of the body that can be expected to sustain most of these injuries, such as knees, elbows, and palms, could be protected with elbow pads, knee pads, and gloves. Some studies have questioned the effectiveness of such protective gear^{3,12} because the force of impact may be transmitted through protective clothing to cause fractures, whereas unprotected soft tissue may absorb the brunt of the injury. Appropriately designed gear should reduce this risk. Perhaps a more likely danger is that protective gear may give skateboarders a false sense of security, fostering more dangerous "tricks."

Because the worst injuries affected older children, who tended to ride in streets and highways, skateboard use in these areas should be prohibited, preferably by state or federal statute. Use of skateboards in the streets and highways poses a high risk of serious injury for at least three reasons. First, and most important, is the proximity to high-speed motor vehicles. That contact with these is likely to result in injuries of high severity is demonstrated by the fact that at least 58% of the CPSC-recorded skateboard-related deaths involved motor vehicles. Second, when skateboarders are in the roadway, traffic speeds are likely to encourage high-speed skating, which increases the chance of serious injury in the case of a tumble or collision. Third, roadways commonly have surface irregularities that readily affect the travel of small skateboard wheels, increasing the likelihood of falls and consequent injury (with or without motor vehicle contact).

Implications

Emergency department physicians need to be aware of the current pattern of skateboard use in the community and of the associated injuries. Continuing expansion of this outbreak would suggest a need for public awareness and perhaps local regulation.

While skateboarding is not a leading cause of death or disability, its prevalence—with a low but real risk of serious injury—merits preventive attention. Recognizing the age-related patterns reported in this study, pediatricians can help prevent serious injury by (1) promoting use of protective gear, (2) discussing skateboard safety with parents and children, (3) discouraging the use of skateboards by infants and toddlers, and (4) lobbying for CPSC and local government regulations, including age-related use guidelines and prohibitions on the use of skateboards on streets and highways.

Data from this study were shared with legislators and concerned citizens during a series of meetings to decide on the content of skateboarding regulations in the home town of one of the authors (K.C.). Several issues arose that are likely to come up in other settings as well, and so they bear mention herein.

A number of people were uncomfortable applying national data to our particular locale. Even more were dismayed that local data are not readily available: about either the prevalence of skateboarding or the prevalence of skateboard-related injuries. The basis of these concerns was that while it is important to prevent serious injuries, enforcement of an elaborate effort to prevent extremely uncommon injuries could not be justified in terms of the costs involved (mainly police effort and skateboarders' perceptions of harassment). Some tried to use bicycling data to argue for skateboarding in the streets (like bikes). It was helpful to point out (1) that policy must be based on the best available data, even when those data are imperfect, (2) that the injury scenarios that emerged from the national data match ones reported by local skateboarders (eg, a concussion from toppling in traffic after a wheel hit

a pebble in the street), and (3) that the causal sequences are different for injuries from (large, flexible-wheeled) bikes and (small, hard-wheeled) skateboards.

Other issues related to the nature of skateboarders, most of whom are predriving adolescents. Parents and legislators identified the need for a variety of organized recreational opportunities for early teens, perhaps including a skateboard park. However, it is fairly expensive to construct an up-to-date facility that would be usable by skaters at a variety of skill levels, which was particularly relevant as it was not clear how many people would use such a facility. Liability issues were also a concern. A number of youngsters reported that they use their skateboards for transportation (eg, from school to work), and argued that avoiding street skating would interfere with this type of use (because local sidewalks are often cracked). Both the adults and teens agreed that any requirements that are both likely to be violated and difficult to enforce uniformly (eg, helmet wearing) are likely to be ineffective; they also could antagonize skaters if the rules are unevenly or punitively enforced. All agreed that the goal must be to set safe skateboarding guidelines that teens can follow and to avoid "criminalizing" any aspect of this basically wholesome pastime.

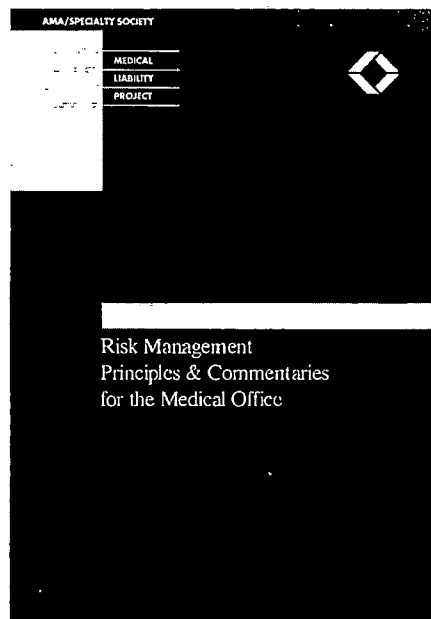
A final area of concern was the effect of skateboarding on pedestrians, which would be maximized by banning skateboarding in the streets. (It was an interaction with pedestrians that led to the arrest of some skateboarders under an ordinance passed during the skateboard injury outbreak of the 1970s, that generated the legislative activity in 1989.)

The outcome of these discussions was revision of the relevant local ordinance to regulate skateboard and rollerskate use in three ways. (1) Such activities cannot collect a crowd. (2) Skaters cannot enter the streets except to cross them (at which time they are considered pedestrians). (3) Sidewalk skating is limited to residential (ie, not business or commercial) areas. No mention is made of helmets. No action has yet been taken on the idea of a skateboard park.

Leon Robertson, PhD, provided helpful comments; Robert Tanz, MD, reviewed the manuscript; and Wanda Harold, Zsazanna Taborn, and Laura R. Gannott gave secretarial support.

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Differences in Infant Mortality by Race, Nativity Status, and Other Maternal Characteristics

Joel C. Kleinman, PhD; Lois A. Fingerhut, MA; Kate Prager, ScD

• The objective of this study was to examine the effects of nativity status (native vs foreign born) and other maternal characteristics (age, parity, education, and marital status) on infant, neonatal, and postneonatal mortality among white and black mothers. The design of this nonrandomized cohort study was based on birth and death certificates. The setting involved live births among US residents (excluding California, Texas, and Washington) in 1983 and 1984. The participants included white mothers with 4.4 million births and black mothers with 926 000 births in single deliveries. There were no interventions. With regard to measurements (the main results), after adjusting for other risk factors, neonatal mortality risk was 22% lower among the black foreign-born mothers than among the black native-born mothers, while among white infants, there was no risk difference by nativity. Relative risks were more similar for postneonatal mortality, ie, 24% lower among black foreign-born mothers and 20% lower among white foreign-born mothers. Combining the several categories of risk factors into three broad maternal risk groups, there was a near-doubling of black and near-tripling of white infant mortality rates between the low and high levels of maternal risk. We concluded that if the infant mortality rate in the low-risk groups could be achieved by the moderate- and high-risk groups, there would be a 30% reduction in infant deaths within each race. Since the black infant mortality rate is twice the white infant mortality rate and black foreign-born mothers have much lower rates than black native-born mothers, it is likely that further improvement is possible among black infants.

(AJDC. 1991;145:194-199)

Racial differences in infant mortality and in low birth weight have been the focus of many epidemiologic analyses. Maternal risk factors responsible for differences in low birth weight among white and black infants were examined in a recent study with the use of 1983 national data.¹ The analysis showed large racial differences even among mothers at low risk of poor pregnancy outcome. Furthermore, the effects of each of several maternal risk factors were found to be stronger among whites than

among blacks. With the recent availability of national files of linked births and infant deaths, we are able in this article to extend the previous analysis to infant mortality. In addition, we focus on another maternal characteristic that has not received much attention—nativity status—that is, whether the mother was foreign born or native born.

Previous reports of pregnancy outcome among foreign-born mothers have been limited to relatively select population subgroups.²⁻⁶ The 1971 through 1973 New York City, NY, data reported by Valanis and Rush^{2,3} showed that black foreign-born women had a lower proportion of low-birth-weight infants than black native-born women. The study by Kessner⁴ used New York City data for 1968 to show significantly higher mean birth weights and lower infant mortality rates among black foreign-born women than black native-born women. In a recent analysis of black foreign- and native-born women in Boston, Mass,⁵ it was observed that the infants of foreign-born mothers experienced greater intrauterine growth than those of native-born mothers. In a 1979 analysis of data from Sweden, Smedby and Ericson⁶ found that the perinatal mortality rate among children born to immigrant mothers was lower than the rate among children born to Swedish mothers. In this study, we used national linked birth and infant death files for 1983 and 1984 to examine racial differences in the effects of maternal sociodemographic risk factors, including nativity status, on infant, neonatal, and postneonatal mortality.

MATERIALS AND METHODS

We combined the 1983 and 1984 national files of linked birth and infant death certificates to investigate the relationships between maternal risk factors and infant mortality. The data were classified by maternal race and place of birth into four categories—black foreign- and native-born mothers and white foreign- and native-born mothers. Mothers who were born outside the 50 United States or the District of Columbia were classified as foreign born. All others (including the 0.2% with an unknown place of birth) were coded as native born. Births in California, Texas, and Washington where education is not on the birth certificate were omitted from the analysis. By excluding these births, 21% of the births to white native-born mothers, 16% of those to black native-born mothers, 49% of the births to white foreign-born mothers, and 12% of the births to black foreign-born mothers were omitted from the analysis. Most of the omitted white foreign-born mothers were of Mexican descent. Despite the large proportion of births excluded, the infant mortality rates based on all births were very similar to those based on births to mothers with known education. For example, the infant mortality rate among white

Accepted for publication August 17, 1990.

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foreign-born mothers was 7.9 per 1000 live births overall compared with 8.1 for those mothers with known education.

In 1983 and 1984, black foreign-born women who resided in large metropolitan counties (population, $\geq 250\,000$) accounted for 93% of the births to black foreign-born mothers. This compares with 63% of the births to black native-born mothers, 78% to white foreign-born mothers, and 43% to white native-born mothers. To ensure that residence was not a confounding factor, this variable (large metropolitan areas vs all other counties) was included as a covariate in the regression analysis. Furthermore, the analysis was repeated for the large metropolitan areas only. Since the results for the restricted analysis were nearly the same as the results for the entire United States, only the latter results are presented.

Only live births in single deliveries (98% of all births) and of known birth order (99.5% of all births) were included in the analysis. The low- and very-low-birth-weight rates were based on births with known birth weights (59.9% of all births).

Multiple logistic regression was used to estimate the effects of each of the maternal characteristics after controlling for the others. Separate analyses were carried out by using five different dependent variables: infant, neonatal, and postneonatal mortality; very low birth weight (<1500 g); and low birth weight (<2500 g). However, because the birth weight results are very similar to those presented earlier,¹ only the detailed results for the three mortality rates are presented in this article. Detailed birth weight results are available on request to the authors. The BMDP logistic regression programs were used.⁷ For comparison with previous results on birth weight,¹ the results of the logistic regressions with mortality as the dependent variable are summarized by presenting directly standardized rates that were determined with the use of the fitted rates from the models and the combined distribution of all births as the standard population. These standardized rates provided an average risk of neonatal, postneonatal, or infant mortality for each maternal characteristic after adjustment for all the other characteristics in the model.

To maintain comparability with previous work,¹ other variables included in this analysis are as follows: maternal education (<12 , 12, 13 through 15, and 16 or more years); marital status (married or not married); age (<13 , 18 and 19, 20 through 29, and 30 years or older); and parity (primiparas or multiparas). High parity was defined as third- or higher-order births to women younger than 25 years and fourth- or higher-order births to women aged 25 years or older. All other multiparous births were considered to be of low parity.

The following three categories of maternal risk summarize these variables: (1) *Low-risk* mothers consisted of married mothers with at least 13 years of education who were either primiparas aged 20 through 29 years or low-parity multiparas aged 20 years or older. (2) *High-risk* mothers included unmarried mothers with less than 12 years of education who were either teenagers, primiparas aged 30 years or older, or high-parity multiparas. (3) The *moderate-risk* group of mothers included all other combinations of maternal characteristics.

RESULTS

Maternal Risk and Nativity

In 1983 and 1984, 7% of both white and black births were to foreign-born mothers. The distribution of births by maternal risk shows that, overall, 11% of black and 28% of white births were at low risk, while 22% of black and 4% of white births were at high risk of poor pregnancy outcome (Table 1). However, the black foreign-born mothers were more likely than the black native-born mothers to be at low risk, ie, 18% compared with 10%, and were much less likely to be at high risk, ie, 10% vs 23%. Among white births, the differences by nativity status were smaller and in the opposite direction. Twenty-nine percent of the births to white native-born mothers vs 23% of the births to white foreign-born mothers were at low risk, and only 4% of the births to white native-born mothers and 7% of the births to white foreign-born mothers were at high risk. Detailed distributions of births by the variables that were

Table 1.—Distribution of Live Births by Maternal Race, Risk, and Nativity Status: United States, 1983 and 1984 Birth Cohorts*

Maternal Risk	% All Mothers Foreign-born Mothers Native-born Mothers		
	All Mothers	Foreign-born Mothers	Native-born Mothers
Black			
Low	10.6	17.6	10.1
Moderate	67.1	72.3	66.8
High	22.2	10.1	23.1
Total	100.0	100.0	100.0
White			
Low	28.3	22.6	28.7
Moderate	67.3	70.7	67.1
High	4.4	6.7	4.2
Total	100.0	100.0	100.0

*The number of black mothers was as follows: all, 926 118; foreign born, 61 900; and native born, 864 218. The number of white mothers was as follows: all, 4 401 338; foreign born, 286 229; and native born, 115 109.

included in the risk categories are given in Table 2.

Black foreign-born women had a 36% lower incidence of low-birth-weight infants and a 32% lower incidence of very-low-birth-weight infants than black native-born women (Table 3). Among white women, the differences in the incidence of low-birth-weight infants by nativity status were smaller and in the opposite direction. The incidence of very-low-birth-weight infants was 11% higher among the foreign- than the native-born women (Table 3).

Black foreign-born mothers also had 28% lower infant mortality rates than the black native-born mothers; 12.4 vs 17.3 deaths per 1000 live births (Table 4). The nativity difference was larger for postneonatal than for neonatal mortality, ie, 37% vs 23%. Among white mothers, however, there was virtually no difference in infant mortality by nativity status, ie, 8.1 vs 8.2 deaths per 1000 live births for foreign- and native-born mothers, respectively—the net result of 6% higher neonatal mortality and 10% lower postneonatal mortality among white foreign- than native-born mothers.

Differences in infant mortality rates by maternal risk categories were larger than differences by nativity status. Among blacks, the infant mortality rate for high-risk mothers was 84% higher than the rate for low-risk mothers, ie, 21.4 vs 11.6 per 1000 live births (Table 4). Among whites, the differences were even larger; the rate for high-risk mothers was 2.7 times the rate for low-risk mothers, ie, 15.4 vs 5.7 per 1000 live births. As a result, the black-white ratio decreased from 2.0 among low-risk mothers to 1.4 among high-risk mothers. For both black and white infants, differences between the low- and high-risk categories were much larger for postneonatal than for neonatal mortality. The postneonatal mortality rates for high-risk mothers, both black and white, were more than three times the rates for low-risk mothers (9.7 vs 3.1 for blacks and 6.5 vs 1.8 for whites). Although the black-white ratio in neonatal mortality was greater among low-risk (2.2) than high-risk (1.3) mothers, for postneonatal mortality, there was only a small difference in the ratios: 1.7 for low-risk vs 1.5 for high-risk mothers (Table 4).

Infant mortality rates for the variables that were included in the risk categorization are shown in Table 5.

Table 2.—Distribution of Live Births by Selected Maternal Characteristics According to Race and Nativity Status of Mother: United States, 1983 and 1984 Birth Cohorts

	Black		White	
	Foreign Born	Native Born	Foreign Born	Native Born
Total No. (%)	61 900 (100.0)	864 218 (100.0)	286 229 (100.0)	115 109 (100.0)
Age and parity				
Primiparas, y				
<18	2.1	9.4	2.1	3.2
18-19	3.6	7.8	3.9	5.2
20-29	21.1	14.0	21.7	23.5
≥30	5.1	1.4	5.2	4.2
Multiparas, y				
<18	0.4	2.6	0.5	0.5
18-19	2.0	6.5	2.2	2.4
20-29	39.1	44.2	39.0	41.3
≥30	26.8	14.0	25.4	19.6
Parity				
Primiparity	31.7	32.6	32.9	36.1
Low multiparity	40.9	36.6	43.5	45.0
High multiparity	27.3	30.7	23.5	18.8
Marital status				
Married	60.0	37.6	82.4	88.1
Not married	40.0	62.4	17.5	11.9
Educational attainment, y				
<12	30.9	34.2	32.9	17.5
12	37.1	42.9	35.3	43.9
13-15	19.0	16.5	16.5	20.6
≥16	13.1	6.3	15.2	18.1
Metropolitan residence status				
Metropolitan counties (250 000+ population)	93.0	62.5	78.1	42.9
All other counties	7.0	37.5	21.9	57.1
Mothers aged 20 y or older				
Total No. (%)	56 936 (100.0)	637 602 (100.0)	261 283 (100.0)	3 647 029 (100.0)
Educational attainment, y				
<12	28.7	23.3	29.4	12.0
12	37.0	47.0	36.1	44.9
13-15	20.0	21.2	17.3	22.8
≥16	14.2	8.6	16.5	20.4

Regression Analysis

Multiple logistic regression analysis was used to examine the effects of individual risk factors after adjusting for all the others. Previous regression results with the use of birth weight as the dependent variable (which did not include nativity status) showed that the effects of individual risk factors—education, marital status, age and parity—were generally stronger among whites than among blacks. The results of multiple logistic regression on birth weight, which included residence and nativity status, were similar (detail not included here). Nativity status was the only factor that had stronger effects among blacks. Black foreign-born women were 36% less likely than black native-born women to have a low-birth-weight baby, whereas the risk of a white foreign-born woman having a low-birth-weight infant was only 10% less than for a white native-born woman (Table 6). Among black mothers, the risk of having a very-low-birth-weight baby was

31% lower for the foreign-born mothers than for the native-born mothers, while among white mothers, there was no difference by nativity status in the risk of having a very-low-birth-weight infant (Table 6).

Similarly, the effects of nativity status on infant mortality were considerably larger for blacks than for whites. The risk of an infant death was 23% lower among the black foreign-born mothers and 8% lower among the white foreign-born mothers as among the native-born mothers. Black foreign-born mothers had 22% lower neonatal and 24% lower postneonatal mortality than their native-born counterparts. Among white mothers, the likelihood of a neonatal death was equal among the foreign- and native-born women, while the risk of a postneonatal death was 20% lower among the foreign-born women (Table 6).

The effects of the other maternal risk factors—education, age, parity, and marital status—on neonatal and postneonatal mortality, unlike those found in the previous

Table 3.—Low- and Very-Low-Birth-Weight Rates by Race and Nativity Status of Mother: United States, 1983 and 1984 Birth Cohorts

	Rate/1000 Live Births*			
	Black		White	
	Foreign Born	Native Born	Foreign Born	Native Born
Low birth weight	75.4	117.4	49.5	47.8
Very low birth weight	15.4	22.6	8.3	7.5

*With known birth weight.

Table 4.—Infant Mortality Rates by Maternal Nativity Status and by Maternal Risk According to Race and Age at Death: United States, 1983 and 1984 Birth Cohorts

	Rate/100 Live Births					
	Black			White		
	Neo-Infant	Post-natal	neonatal	Neo-Infant	Post-natal	neonatal
All infants	17.0	10.6	6.3	8.2	5.2	3.0
Maternal nativity status						
Foreign born	12.4	8.3	4.1	8.1	5.5	2.7
Native born	17.3	10.8	6.5	8.2	5.2	3.0
Maternal risk						
Low	11.6	8.4	3.1	5.7	3.9	1.8
Moderate	16.3	10.6	5.7	8.8	5.5	3.3
High	21.4	11.7	9.7	15.4	8.9	6.5

birth weight analysis,¹ were not consistently greater among whites than blacks (Table 7). In particular, controlling for all other factors, the effects of education on postneonatal mortality were similar for whites and blacks: mothers with less than 12 years of education were twice as likely as those with 16 or more years to have a postneonatal death. The neonatal mortality risk ratios between the lowest and highest educational levels were smaller: 1.4 for whites vs 1.1 for blacks.

Age and parity effects on neonatal and postneonatal mortality were not consistent among whites and blacks. Standardized neonatal mortality rates were high among white and black multiparous teenagers younger than 18 years and primiparas aged 30 years or older. White primiparas younger than 18 years and multiparas aged 18 and 19 years also had high rates. Excess risks among teenagers (relative to 20- to 29-year-old multiparas) were greater among whites than blacks. On the other hand, excess risk was greater for black than white primiparas aged 30 years or older.

Standardized postneonatal mortality rates were highest for multiparous teenagers in both race groups, with excess risk greater for whites than blacks. Furthermore, in contrast to neonatal mortality, both white and black primiparous mothers aged 30 years or older had among the lowest standardized postneonatal mortality rates. It is of interest to note that primiparous teenagers aged 18 and 19 years had the lowest standardized neonatal and postneonatal rates among blacks.

High parity generally showed similar effects on neonatal and postneonatal mortality for whites and blacks (relative risk [RR] range, 1.3 to 1.4). The effects of marital status on neonatal and postneonatal mortality were slightly larger

Table 5.—Infant Mortality Rates by Race and Other Maternal Factors: United States, 1983 and 1984 Birth Cohorts

	Rate/1000 Live Births					
	Black			White		
	Neo-Infant	Post-natal	neonatal	Neo-Infant	Post-natal	neonatal
Total	17.0	10.6	6.3	8.2	5.2	3.0
Age and parity						
Primiparas, y						
<18	17.7	10.7	7.0	14.0	8.6	5.4
18-19	13.9	9.1	4.9	10.3	6.4	3.9
20-29	14.1	9.9	4.1	6.6	4.5	2.1
≥30	19.0	15.7	3.3	7.2	5.4	1.8
Multiparas, y						
<18	29.1	15.9	13.1	20.5	11.0	9.5
18-19	22.9	12.1	10.7	15.4	7.8	7.6
20-29	17.1	10.2	6.9	9.0	5.5	3.6
≥30	15.9	11.3	4.6	7.2	5.0	2.2
Parity						
Primiparity	15.3	10.2	5.0	7.9	5.2	2.6
Low multiparity	15.7	9.8	5.9	7.4	4.7	2.8
High multiparity	20.3	12.1	8.2	10.7	6.5	4.2
Marital status						
Married	14.0	9.4	4.6	7.5	4.9	2.7
Not married	18.9	11.4	7.4	13.0	7.8	5.2
Educational attainment, y						
<12	20.2	11.2	9.0	12.6	7.0	5.6
12	16.2	10.6	5.6	8.1	5.3	2.8
13-15	14.3	10.2	4.1	6.7	4.5	2.2
≥16	12.1	9.2	2.9	5.7	4.0	1.7
Metropolitan residence status						
Metropolitan counties (250 000+ population)	17.0	10.7	6.2	7.9	5.2	2.8
All other counties	16.9	10.4	6.5	8.4	5.3	3.2
Mothers aged 20 y or older						
Total	16.3	10.5	5.8	7.6	4.9	2.7
Educational attainment, y						
<12	20.1	10.9	9.1	11.6	6.4	5.2
12	16.1	10.7	5.4	7.8	5.1	2.6
13-15	14.2	10.1	4.1	6.7	4.5	2.2
≥16	12.1	9.2	2.9	5.7	4.0	1.7

Table 6.—Adjusted Odds Ratios Among Foreign-born Mothers for Birth Weight and Infant Mortality: United States, 1983 and 1984 Birth Cohorts*

	Black			White		
	Odds Ratio†	95% CI		Odds Ratio†	95% CI	
		Lower	Upper		Lower	Upper
Low birth weight	0.64	0.62	0.66	0.90	0.89	0.92
Very low birth weight	0.69	0.65	0.74	0.99	0.95	1.03
Infant mortality	0.77	0.72	0.83	0.92	0.88	0.96
Neonatal mortality	0.78	0.71	0.86	0.99	0.94	1.05
Postneonatal mortality	0.76	0.67	0.86	0.80	0.74	0.86

*CI indicates confidence interval.

†Odds ratios are for foreign-born mothers; reference group is native-born mothers. Variables included in the adjustment are age, parity, education, marital status, and metropolitan status.

for white than for black mothers (RR range, 1.4 vs 1.2 to 1.3). There were no differences by metropolitan residence in the risk of neonatal death. However, whites outside the large metropolitan areas had a somewhat greater risk of a postneonatal death (RR, 1.1).

COMMENT

In this analysis, the 1983 and 1984 national linked files of births and infant deaths were used to examine the differentials in infant mortality by race, nativity status, and other maternal characteristics. Black foreign-born mothers had 23% lower neonatal and 37% lower postneonatal mortality rates than their native-born counterparts. After adjustment for age, parity, education, marital status, and residence, the differential remained about the same for neonatal mortality but was reduced to 24% for postneonatal mortality. Among white women, the foreign-born mothers had 6% higher neonatal mortality and 10% lower postneonatal mortality rates. After adjustment for other risk factors, white foreign-born women had a 20% lower risk for postneonatal mortality, but similar risks for neonatal mortality compared with that for white native-born women.

The low risk of postneonatal death for both white and black foreign-born women raises the possibility of underreporting. It is possible, for example, that foreign-born mothers with sick infants return to their countries of origin before the infant's death. It is difficult to investigate this possibility, but it does not seem entirely plausible. Although access to preventive care may be problematic, treatment of life-threatening illness is probably as readily available in the United States as in most countries from which the foreign-born mothers have migrated.

Data from the 1983 Current Population Survey show that the black foreign-born population was of a higher socioeconomic status than the black native-born population, but that the reverse was true for the white population.⁸ Median annual earnings were 22% higher for the black foreign-born mothers than for the black native-born mothers; family incomes of more than \$35 000 were reported more by black foreign-born mothers than by black native-born mothers (30% vs 17%). Consistent with what the birth certificate data showed, there were proportionately more foreign-born mothers than native-born mothers who at-

Table 7.—Standardized Infant Mortality Rates by Race and Other Maternal Factors: United States, 1983 and 1984 Birth Cohorts*

	Rate/1000 Live Births					
	Black			White		
	Neo-Infant natal	Post-neonatal		Neo-Infant natal	Post-neonatal	
Nativity status						
Foreign born	12.7	8.6	4.1	7.7	5.1	2.6
Native born	16.4	11.0	5.4	8.4	5.1	3.3
Age and parity						
Primiparas, y						
<18	15.9	11.1	4.8	10.4	6.8	3.6
18-19	13.6	9.4	4.2	9.3	5.7	3.6
20-29	15.6	11.1	4.6	7.5	4.8	2.7
≥30	23.4	19.1	4.3	9.0	6.3	2.7
Multiparas, y						
<18	24.6	16.0	8.7	15.1	8.7	6.4
18-19	19.5	11.8	7.7	12.2	6.5	5.8
20-29	15.9	10.2	5.7	8.2	4.8	3.5
≥30	16.1	11.8	4.3	7.7	5.0	2.7
Parity						
Low	15.2	10.3	4.9	7.8	4.8	3.0
High	19.6	12.9	6.7	10.5	6.4	4.1
Marital status						
Married	15.2	10.3	4.9	7.8	4.8	3.0
Not married	19.1	12.5	6.5	10.8	6.6	4.2
Educational attainment, y						
<12	17.4	9.9	7.5	10.9	6.0	4.9
12	15.6	10.3	5.3	8.6	5.5	3.0
13-15	14.4	10.1	4.3	7.5	4.9	2.6
≥16	12.9	9.3	3.7	6.6	4.3	2.2
Metropolitan residence status						
Metropolitan counties (250 000+ population)	16.1	11.0	5.1	8.3	5.1	3.1
All other counties	15.9	10.7	5.2	8.5	5.2	3.3

*Rates are directly standardized by using the distribution of all live births and the fitted values from multiple logistic regression analyses of neonatal and postneonatal mortality.

tained the higher levels of education. Among the white population, the differences were somewhat smaller and were in the opposite direction.

Behavioral, cultural, and nutritional factors that might account for the lower infant mortality among the black foreign-born mothers are difficult to ascertain. One study of women receiving prenatal care in Boston (Mass) City Hospital⁹ showed that the black foreign-born women were less likely than the black native-born women to smoke cigarettes or to abuse drugs. Unfortunately, there are no national data available to determine whether smoking prevalence differs by nativity and race. It is known, however, that smoking rates in the Caribbean countries (where most black foreign-born women are from) are relatively low compared with that in the United States.⁹ Assuming

that this positive health practice continues after the women migrate to the United States, reduced smoking could explain some portion of the differences by nativity in infant mortality and low birth weight.

The study of migrant populations is difficult because their health status could introduce opposing types of bias. First, the fact that they left their country of origin suggests that migrants may be healthier (both physically and mentally) than those remaining in their country or even their counterparts in the country to which they migrate. On the other hand, the stresses of migration itself are not inconsequential and may adversely affect the migrant population's health.¹⁰ In any case, it is of interest to note that black foreign-born women in this country are not generally recent immigrants. Based on our analysis of 1980 census data, about 60% of the black foreign-born women aged 15 to 24 years and 70% of those aged 25 to 34 years lived in the United States for more than 5 years.¹¹ Further study of the black foreign-born population could yield valuable clues for prevention strategies.

With respect to the other risk factors examined, there are several points that are worth noting. In particular, black primiparas aged 18 and 19 years had the lowest infant mortality rates of all the age-parity groups for black mothers. Even black primiparas younger than 18 years did not have unusually high rates. It is the multiparous teenagers, both black and white, who have the highest rates, but they account for only a small proportion (9% of black and 3% of white) of births. Thus, although teenage childbearing represents a serious social problem, it does not account for the twofold black-white differential in infant mortality. If all teenage births are excluded, the black infant mortality rate would decline by 4%, while the white infant mortality rate would decline by 7%, thereby slightly increasing the black-white ratio.

Combining the several categories of risk factors into three broad maternal risk groups, there was a near-doubling of black and near-tripling of white infant mortality rates between the low and high levels of maternal risk. If the infant mortality rate in the low-risk groups could be achieved by the moderate- and high-risk groups, there would be a 30% reduction in infant deaths within each race. Since the black infant mortality rate is twice the white rate and foreign-born black mothers have much lower rates than native-born black mothers, it is likely that further improvement is possible among blacks.

One of the important differences among these maternal risk groups is their access to preventive health care during the prenatal and infant period. Data from birth certificates show that 91% of the low-risk white women and 82% of the low-risk black women began prenatal care in the first

trimester compared with 47% and 44% among the high-risk white and black women, respectively. Data on health care utilization during infancy also show large differentials by mother's education.¹² Interventions to reduce the disparities in infant mortality need to include improving access to care during these critical periods. Yet, the large social class differentials in infant mortality, even in countries with universal access to health care,¹³⁻¹⁵ suggest that having access to services is not sufficient. Aggressive outreach and educational efforts are also needed to prevent infant deaths in disadvantaged groups.

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Retinopathy of Prematurity in Infants With Cyanotic Congenital Heart Disease

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● We undertook a study of premature infants with cyanotic congenital heart disease to determine whether these infants develop retinopathy of prematurity despite a persistent hypoxemic state. Using the computerized registry of the neonatal intensive care unit of Vanderbilt University Medical Center, Nashville, Tenn, we identified six premature infants (<37 weeks' gestational age, with birth weights of 1100 to 2050 g) with cyanotic congenital heart disease who survived the neonatal period and underwent ophthalmologic evaluation. Review of their charts revealed that three of six infants developed retinopathy of prematurity (two had grade 1 and one had grade 3 disease), but none required treatment. Our data support the findings of other investigators that elevated arterial oxygen tension is not the sole factor leading to the development of retinopathy of prematurity. Premature infants with cyanotic congenital heart disease can develop retinopathy of prematurity despite persistent hypoxemia. Cyanotic premature infants should be screened for retinopathy of prematurity with the same thoroughness as other premature infants. (*AJDC*. 1991;145:200-203)

Retinopathy of prematurity (ROP) remains a common cause of blindness and serious visual impairment in premature infants.¹ The etiology of ROP appears to be multifactorial, and investigators have identified such diverse risk factors as sepsis, gestational age, apnea, ambient light levels, reduced vitamin E levels, and xanthine administration.²⁻⁸ The role of oxygen in the etiology of this disease remains controversial. Since the 1942-1954 epidemic of ROP, a relationship has been assumed between arterial oxygen tension and this disorder, but the nature of this relationship has been difficult to confirm in prospective clinical studies. Premature infants with cyanotic congenital heart disease (CCHD) are unable to develop elevated arterial oxygen tensions despite supplemental oxygen. For this reason, the risk of ROP in premature in-

fants with CCHD has been thought to be very low, and only two isolated cases have been reported.^{9,10}

The combination of CCHD and prematurity is uncommon, and the number of patients available for study is further reduced by the fact that many premature infants with CCHD do not survive. The objective of this study was to identify premature infants with CCHD who have been cared for in the neonatal intensive care unit of Vanderbilt University Medical Center, Nashville, Tenn, and to determine the incidence of ROP in these patients.

PATIENTS AND METHODS

The computerized registry of the neonatal intensive care unit at Vanderbilt University Medical Center was used to identify premature infants under 37 weeks' gestational age.¹¹ A total of 6401 premature infants were admitted to the neonatal intensive care unit over a 15-year period from January 1, 1974, through December 31, 1988. Of this population, 86 infants were identified as having congenital heart defects (other than patent ductus arteriosus). Of the 86 premature infants identified with congenital heart disease, 64 were acyanotic and 22 were cyanotic. Five of these cyanotic infants died in the early postnatal period. Seventeen infants survived the early neonatal period, and, of these, 11 had such a high birth weight (>2000 g) that ophthalmologic consultation was not requested. In one case, ophthalmologic consultation was requested in a patient with a birth weight of 2050 g. Although 2050 g is greater than the usual birth-weight criterion at our institution (2000 g), the neonatologist thought ophthalmologic evaluation was indicated because of the large amount of supplemental oxygen this infant required.

Six infants underwent complete ophthalmologic evaluation between the sixth and ninth weeks of life by a retinal specialist (S.S.F.) trained in the recognition of ROP. In patients found to have any features consistent with ROP or incomplete retinal vascular development, serial examinations were performed every 2 to 3 weeks. Because many of these infants were critically ill and required cardiac surgery, the exact timing of the examination was dependent on the cardiovascular stability of the infants. The medical records of these six patients were reviewed.

RESULTS

The clinical findings are summarized in the Table. The birth weights in our study group ranged from 1100 to 2050 g, with a mean of 1500 g. The gestational ages of the infants ranged from 26 to 34 weeks, with a mean of 30 weeks. There were four male and two female infants. Each of the infants had a cyanotic congenital heart lesion, resulting in a mean arterial oxygen tension lower than 55 mm Hg despite the administration of supplemental oxygen. All the infants required intubation and mechanical ventilation. All six infants underwent a palliative procedure,

Accepted for publication October 2, 1990.

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Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, May 3, 1989, and at the Third World Congress of Pediatric Cardiology, Bangkok, Thailand, November 30, 1989.

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Clinical Findings in Infants With Cyanotic Congenital Heart Disease With and Without ROP*

Patient No./Sex	Birth Weight, g	Gestational Age, wk	Cardiac Diagnosis	Cardiac Procedure	Duration of Oxygen Supplementation, d	Fraction of Inspired Oxygen, %	PO ₂ , mm Hg†	PcO ₂ , mm Hg†	pH†	No. of Blood Gas Determinations	Ophthalmologic Findings
1/M	1400	29	Transposition of the great arteries, ventricular septal defect	Ballon atrial septostomy at age 1 d	33	30 to 100	46 ± 12	37 ± 10	7.41 ± 0.08	57	No ROP; examinations at 8 and 11 wk
2/M	1100	26	Transposition of the great arteries	Atrial septectomy at age 3 wk	42	24 to 100	45 ± 14	39 ± 10	7.39 ± 0.08	164	No ROP; examinations at 8 and 12 wk
3/F	1400	34	Tricuspid atresia, ventricular septal defect	Aorta to pulmonary artery shunt at age 2 wk	35	30 to 100	38 ± 12	37 ± 10	7.41 ± 0.09	59	No ROP; examinations at 6 and 12 wk
4/M	1400	30	Transposition of the great arteries, ventricular septal defect	Ballon atrial septostomy at age 8 wk	40	30 to 100	38 ± 12	44 ± 22	7.38 ± 0.13	172	Stage 1 ROP at 7 wk, resolved at 9 wk
5/M	2050	33	Tricuspid atresia, ventricular septal defect	Aorta to pulmonary artery shunt at age 1 mo	31	30 to 100	49 ± 12	44 ± 9	7.35 ± 0.08	42	Stage 1 ROP at 6 wk, resolved at 8 wk
6/F	1650	28	Transposition of the great arteries, coarctation of the aorta	Repair of coarctation of the aorta and placement of pulmonary artery band at age 1 wk	42	25 to 100	55 ± 29	44 ± 10	7.36 ± 0.06	109	Stage 3 ROP at 8 wk, patient died before another examination could be performed

*ROP indicates retinopathy of prematurity.

†Values are mean ± SD.

either surgical or with interventional catheterization, intended to improve oxygenation and/or congestive heart failure. Following these palliative procedures, arteriovenous mixing persisted and the infants remained hypoxemic. None of the infants had sustained hyperoxia, which we defined as arterial oxygen tension greater than 100 mm Hg.

Of the six patients in the study group, four had transposition of the great arteries with or without ventricular septal defects and two had tricuspid atresia.

Three patients developed ROP and three did not. In each group there were two infants with transposition and one with tricuspid atresia, and in each group there were two male and one female infants. Birth weights of the patients who developed ROP were 1400, 1650, and 2050 g; birth weights of the patients who did not develop ROP were 1100, 1400, and 1400 g.

During the initial evaluation of the three patients who

did not develop ROP, incomplete retinal vascular development was found, and the patients were examined serially until each reached vascular maturity. Three patients did develop ROP. Patient 4 was noted, 7 weeks after birth, to have arteriovenous anastomoses posterior to the ora serrata and a demarcation line in both eyes, placing the retinopathy at stage 1 by the international classification of ROP.¹² When the patient was reexamined at age 9 weeks, the ROP had resolved and the retinal vasculature had reached maturity. Patient 5 was found to have a demarcation line in zone 3 of each eye at age 6 weeks, consistent with stage 1 disease. When the patient was reexamined at 8 weeks, the demarcation line had resolved and the retinal vasculature had completed its development. Patient 6 was first examined at 8 weeks of age. She was found to have peripheral arteriovenous anastomoses in the right eye. In the left eye there were arteriovenous anastomoses and neovascular tufts in the superotemporal retina, classifying

this as stage 3 retinopathy. The patient died before another examination could be performed. The eyes were not available for postmortem examination.

The mean arterial oxygen tension of the study patients ranged from 38 to 54 mm Hg (Figure). The infants who developed ROP had mean arterial oxygen tensions similar to those of infants who did not develop ROP (47.2 vs 43.1 mm Hg). The duration of supplemental oxygen administration varied from 30 to 50 days, with the fraction of inspired oxygen ranging from 100% oxygen to room air in all patients. The mean duration of oxygen administration was 38 ± 6 days in infants who developed ROP and 37 ± 5 days in infants who did not develop ROP. The mean arterial P_{CO_2} of the study patients ranged from 36 to 44 mm Hg. The mean arterial carbon dioxide levels of the infants who developed ROP and those who did not were similar (43.2 ± 2.3 vs 37.7 ± 1.4 mm Hg). Mean pH values of these patients ranged from 7.35 to 7.41. The mean pH values were similar for infants who did and did not develop ROP (7.36 ± 0.02 vs 7.40 ± 0.02).

All patients received supplemental vitamin E therapy. All patients underwent transfusions as needed to maintain a hematocrit of at least 0.40 to maximize oxygen delivery.

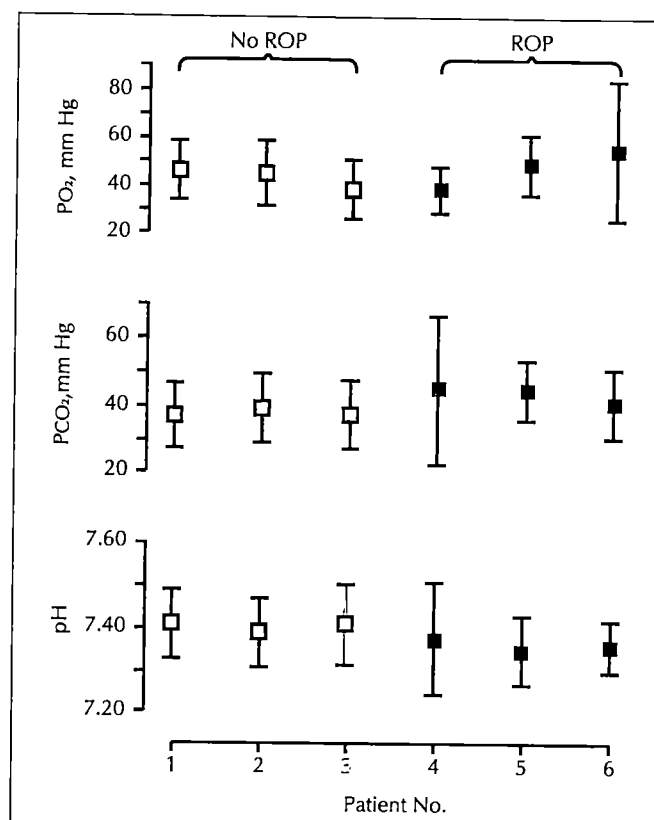
COMMENT

Since Terry¹³ initially described the cicatricial stages of ROP (formerly known as retrolental fibroplasia) in 1942, there have been extensive efforts to identify the agent or agents responsible for this blinding process. Since the middle 1950s, the administration of oxygen has been implicated as one potential causative factor in the development of ROP.^{2,14,15} The incidence of ROP has been found to correlate more closely with the duration of oxygen administration than with the concentration of inspired oxygen.¹⁶

In the Cooperative Study of Retrolental Fibroplasia and the Use of Oxygen, Kinsey and coworkers^{16,17} found that the incidence of ROP increased with duration of exposure to oxygen. In that prospective multicenter clinical trial, premature infants with birth weights under 1500 g were assigned to receive either "routine oxygen" therapy, 28 days of supplemental oxygen with fractions of inspired oxygen exceeding 50%, or "curtailed oxygen" therapy, supplemental oxygen with fractions of inspired oxygen below 50%, administered only as needed to relieve anoxia. The incidence of ROP was significantly greater in the routine oxygen group. Although arterial oxygen tension measurement techniques were not in use at the time the study was conducted, it is reasonable to assume that the infants in the routine oxygen group had elevated arterial oxygen tensions. Thus, a relationship has been presumed between elevated arterial oxygen and the incidence of ROP.

Since the advent of routine clinical arterial oxygen tension measurement, there have been attempts to correlate arterial oxygen levels and the development of ROP, but the results have been contradictory. In a case-control study of 14 very-low-birth-weight infants (<1500 g), Yu and coworkers¹⁸ found that the development of ROP was not related to arterial oxygen tension by intermittent sampling. In contrast, Shahinian and Malachowski¹⁹ reported a correlation between the severity of ROP and duration of elevated capillary oxygen tension after the first week of life. In a prospective study, Prendiville and Schulenburg²⁰ noted that episodes of hyperoxia were significantly associated with the development of ROP.

The role of oxygen in the development of ROP has also been studied in animal models. Patz et al and²¹ Ashton et al^{22,23} have characterized the response of the retinal blood



Mean arterial oxygen and carbon dioxide tensions and pH of six premature infants with cyanotic congenital heart disease with (patients 1 through 3) or without (patients 4 through 6) retinopathy of prematurity (ROP).

vessels of the immature retina in a kitten model of ROP. In a hyperoxic environment, the immature retinal blood vessels of the kitten undergo profound constriction and vaso-obliteration. When the experimental animal is then returned to room air, a secondary response of vasoproliferation and neovascularization occurs. This process has been considered analogous to the early stages of ROP. However, the cicatricial, advanced stages of ROP are not seen in this experimental model. Gole et al²⁴ and other investigators have noted important differences between the kitten model of oxygen-induced retinopathy and human ROP. Flower,²⁵ studying a beagle puppy model of ROP, produced cicatricial ROP when the animals were pretreated with a prostaglandin-synthetase inhibitor, which blocked the constriction of blood vessels caused by hyperoxia.

Oxygen exposure and hyperoxia have been considered important antecedents to the development of ROP. The occasional reports of this disease in premature and full-term infants who have not received supplemental oxygen²⁶⁻²⁸ and in infants with CCHD^{9,10} have been difficult to reconcile with these concepts.

The fetus with a cyanotic congenital heart lesion has a normal arterial oxygen level because the placenta, rather than the lungs, supplies oxygenated blood. Shortly after birth, however, the nascent functioning of the lungs combined with the closure of the ductus arteriosus and the foramen ovale completes the transformation to the postnatal circulation. At this time the infant with a cyanotic congenital heart lesion develops cyanosis.

In infants with CCHD, the blood flowing out through the aorta to the body is a mixture of deoxygenated blood from the systemic venous return and oxygenated blood

from the pulmonary venous return. When these infants are given supplemental oxygen, the oxygen tension in the blood returning from the lungs may be increased, but, because of the mixing with desaturated blood, the aortic oxygen tension rises only slightly. For the arterial P_{O_2} to rise above 100 mm Hg, the hemoglobin must be more than 96% saturated with oxygen. Admixture with even a small amount of desaturated blood precludes arterial oxygen tensions over 100 mm Hg. Thus, in infants with CCHD, despite oxygen supplementation, the arterial oxygen tension remains lower than normal. In contrast, in infants with normal hearts, the systemic blood flow consists solely of blood returning from the lungs, and supplemental oxygen can raise the arterial oxygen concentrations well above normal.

There is some evidence that episodes of hypoxemia may be a risk factor for the development of ROP. Katzman and colleagues²⁹ compared a group of patients who had severe ROP with a group of patients who had less severe ROP and found that the patients with the more severe disease had a significantly higher number of hours with a P_{O_2} below 50 mm Hg. Flynn and coworkers²⁸ reported that retinal arteriolar constriction was more commonly found in hypoxic premature infants than in hyperoxic infants. Shohat and coworkers,³ in a retrospective multivariate analysis, identified an association between the number of episodes of hypoxemia and the development of ROP in infants weighing less than 1250 g.³ However, an association between hypoxia and ROP has not been demonstrated in all clinical studies.

Episodes of both hypercarbia and hypocarbia were found by Shohat and coworkers³ to be associated with the development of ROP. Hypercarbia was also noted to be a risk factor for the development of ROP in a retrospective multivariate analysis by Bauer and Widmayer.³⁰ However, in a subsequent study, Brown and coworkers³¹ found that P_{CO_2} was not a risk factor. Acidosis was also identified as a risk factor by Prendiville and Schulenburg.²⁰

Premature infants with CCHD present a unique opportunity to study the possibility that hyperoxia is only one of a complex array of factors that lead to the development of ROP. The anatomic cardiac abnormalities in these infants preclude prolonged episodes of hyperoxia, despite supplemental oxygen administration and mechanical ventilation. The infants in our study population were persistently hypoxemic, but in general they had normal arterial carbon dioxide levels and pH values. Despite prolonged hypoxemia, three of six infants developed ROP. We speculate that hypoxemia alone, identified as a risk factor for the development of ROP by Katzman et al²⁹ and Shohat et al,³ may have contributed to the development of ROP in these cyanotic infants.

The persistent hypoxemia of CCHD does not appear to protect an infant from the development of ROP. Premature infants with CCHD should be monitored for the development of ROP just as are premature infants with normal hearts. Our data support the finding of other investigators that arterial oxygen tension is not the sole factor leading to the development of ROP.

This study was supported in part by an unrestricted grant from Research to Prevent Blindness Inc, New York, NY.

We thank Robert Cotton, MD, and Susan Bigham for their assistance.

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Unsuspected Cocaine Exposure in Young Children

Sigmund J. Kharasch, MD; Deborah Glotzer, MD; Robert Vinci, MD; Michael Weitzman, MD; James Sargent, MD

● **Objective:** To determine the prevalence of cocaine exposure among preschool children with clinically unsuspected signs and/or symptoms.

Design: Prevalence study.

Setting: Pediatric emergency department in an inner-city hospital.

Participants: 250 children aged 2 weeks to 5 years who underwent urine assays for cocaine prior to discharge from the emergency department.

Interventions: None.

Measurements/Main Results: Six (2.4%) of the 250 urine assays (95% confidence interval, 0.5% to 4.3%) were positive for benzoylecgonine, the major urinary cocaine metabolite. Four of the positive urine assays were from children younger than 1 year and all children with positive urine assays were younger than 24 months. None of these children presented with a complaint or was identified as having clinical problems currently associated with childhood exposure to cocaine. Possible exposure routes include breast-feeding, intentional administration, accidental ingestion of cocaine or cocaine-contaminated household dust via normal hand-to-mouth activity, and passive inhalation of "crack" vapors.

Conclusion: Among the inner-city children served by this hospital, significant numbers of infants and young children are being exposed to cocaine, and this exposure occurs in a clinically unsuspected population.

(AJDC. 1991;145:204-206)

Cocaine use has increased dramatically during the past decade. While the medical complications of cocaine use have been frequently reported in the adult population, problems arising from cocaine exposure in young children have only recently been recognized. While many reports have focused on complications of prenatal exposure,¹⁻⁶ several recent reports have identified complications of exposure, including seizures,⁷ arrhythmias,⁸ and hypertension,⁹ in infants and young children.

Data on the prevalence of cocaine exposure in the pediatric population are only now appearing. The National High School Senior Survey¹⁰ in 1987 revealed a prevalence of cocaine use of 15% to 20%. In a recent retrospective

review of clinically indicated serum and urine toxicologic screens of 1120 patients at a children's hospital, 52 patients (4.6%) had specimens that contained cocaine and/or cocaine metabolite.¹¹ Intrauterine exposure to cocaine is occurring with especially high frequency. Seventeen percent of pregnant women enrolled in prenatal care at Boston (Mass) City Hospital were found to have used cocaine at least once during pregnancy.¹²

In reports that describe clinical problems associated with cocaine exposure among young children, the routes of exposure include breast-feeding,⁹ accidental ingestion,^{8,13} and intentional administration.⁷ Passive inhalation of crack vapors in children who are in close proximity to aerosolized cocaine has also been implicated as a possible exposure route.¹⁴ While clinical cocaine toxicity may occur from environmental exposure, cases of asymptomatic children with positive cocaine screens have also been reported by the above routes.^{11,15}

To our knowledge, no studies have systematically evaluated the prevalence of cocaine exposure in young children beyond the perinatal period. Given the high prevalence of cocaine use in adults at our hospital, we hypothesized that cocaine exposure may occur in significant numbers of young children and may occur in patients with clinically unsuspected signs and/or symptoms.

PATIENTS AND METHODS

This study was conducted in the pediatric emergency department at Boston City Hospital during a 6-week period. Boston City Hospital is a 434-bed acute-care teaching hospital. There are approximately 24 000 annual visits to the pediatric emergency department, which provides service to patients aged 17 years or younger.

Parents and their children aged 2 weeks to 5 years who presented to the pediatric emergency department for care were eligible for this study. Children were excluded if they presented with any of the following: (1) acute life-threatening emergencies; (2) any history suggestive of cocaine exposure, ie, seizures, chest pain, or cocaine use by a caretaker; or (3) severe diaper rash precluding use of a urine bag. All eligible patients had the following data abstracted from their medical records: age, race, vital signs, insurer status, chief complaint, history of breast-feeding, and final diagnosis.

Parents were requested to participate in a study of children's exposure to environmental toxins, and anonymity was assured. If parents asked what environmental toxins were being investigated, they were informed that we were studying children's exposure to cocaine and antibiotics (antibiotics were being investigated as part of a concurrent emergency department study). Anonymity was ensured by a preassigned study number. Verbal consent was obtained for all children entered into the study. It was not possible to identify any child after the urine was assayed.

Accepted for publication September 4, 1990.

From the Department of Pediatrics, Boston (Mass) City Hospital, and Boston University School of Medicine.

Presented in part at the 30th Annual Meeting of the Ambulatory Pediatric Association, Anaheim, Calif, May 10, 1990.

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Characteristics of Patients With Positive Cocaine Screens

Patient No./Age, mo	Complaint	Vital Signs			Diagnosis
		Temperature, °C	Pulse, Beats/Min	Respiratory Rate, Breaths/Min	
1/1	Cough	36.7	120	40	Pneumonia
2/4	Wheezing	37.9	120	32	Reactive airway disease
3/5	Social evaluation*	37.7	132	32	Otitis media
4/9	Fever	39.8	168	52	Bronchiolitis
5/22	Fever	39.3	160	36	Acute febrile illness
6/19	Trauma	37.6	140	36	Laceration

*Physical examination for placement by the Department of Social Services.

The study was approved by the Human Studies Committee of Boston City Hospital.

The urine samples were refrigerated overnight and transported to a commercial laboratory for analysis. All urine samples were screened within 24 hours by the enzyme-multiplied immunoassay technique for benzoylecgonine, the major metabolite of cocaine, in accordance with the quality assurance guidelines of the American College of Pathology.¹⁶ All positive urine sample findings were confirmed by gas chromatography/mass spectrometry, thin-layer chromatography, or repeated enzyme-multiplied immunoassay technique, depending on the quantity of urine obtained. The threshold for detection of benzoylecgonine in urine is 300 ng/mL.

We performed χ^2 analysis and Fisher's Exact Test to test the statistical significance of differences in response rates and rates of cocaine positivity by characteristics of the children.

RESULTS

Four hundred ninety-four patients were eligible for the study. The parents of 18 of these children refused participation. Of the 476 who agreed to participate, urine was obtained from 250 children (53%) prior to discharge from the emergency department. There were no significant differences between those children whose parents refused to participate and those who participated or between children who voided and those who did not with regard to race, gender, breast-feeding history, insurer status, or diagnosis (respiratory vs nonrespiratory illness). The mean age of the children from whom urine was obtained was 23 months (age range, 2 weeks to 5 years; 40% were younger than 1 year); 59% were male and 53% were black. Six (2.4%) of the 250 urine samples (95% confidence interval [CI], 0.5% to 4.3%) tested positive for benzoylecgonine (one result was reconfirmed by gas chromatography/mass spectrometry, one by thin-layer chromatography, and four by repeated enzyme-multiplied immunoassay technique). The characteristics of the patients with positive urine sample findings are shown in the Table. The cocaine-positive and cocaine-negative groups did not differ with regard to race, gender, breast-feeding history, insurer status, or diagnosis. Although rates of cocaine positivity did not differ significantly by age, the trend was for younger children to have higher rates of exposure (3.8% of children aged 2 weeks to 1 year; 4.4% of children aged 1 to 2 years; and no children aged 2 to 5 years). Of the children with positive urine assays, only one child, a 1-month-old boy, was currently being breast-fed.

COMMENT

In this study, 2.4% of infants and young children presenting to the pediatric emergency department of an urban, public hospital had laboratory evidence of cocaine

exposure at the time of the visit. The observed rate of cocaine exposure in these young children was likely due, in large part, to the prevalence of cocaine use among their caretakers. A recent study documented that as many as one in five inner-city women seeking prenatal care at the same institution used cocaine during pregnancy.¹²

Although rates of cocaine positivity did not vary significantly by age, four of six children in this study with positive urine assays for cocaine were younger than 1 year and all were younger than 24 months. The lack of a significant association between cocaine positivity and children's age may well reflect sample size constraints. Younger children, being less mobile, may be at increased risk for exposure to parents smoking crack nearby or may be at increased risk for accidentally ingesting cocaine or cocaine-contaminated household dust by virtue of normal hand-to-mouth activities of children of this age. It is also possible that cocaine was intentionally administered to some or all of these children. While these children did not have symptoms, younger children have less plasma cholinesterase to metabolize cocaine and are also at greater risk for cocaine toxicity at a given exposure level.¹⁷ Passive inhalation has been suggested as the route of exposure in recent anecdotal reports,^{14,15} and the aerosolized route of exposure is known to occur with other drugs, including marijuana and nicotine.¹⁸⁻²⁰

Children with a history or clinical presentation suggestive of cocaine exposure were excluded from participation in this study so that the findings were limited to unsuspected exposures. None of the participants presented with currently recognized signs of cocaine exposure in children. It is possible, however, that infants and young children exposed to cocaine may suffer from subtle, less noticeable, or unrecognized problems, such as undetected cardiac dysrhythmias, altered gastrointestinal functioning, or neurobehavioral changes. In addition, these findings raise many critical unanswered questions regarding the possible long-term effects of repeated cocaine exposure on the physical, cognitive, and behavioral development of preschool children. Until the consequences of acute and chronic cocaine exposure are more completely understood, it is difficult to determine the implications for clinical practice and social policy of the unexpectedly high rates of exposure to cocaine found in this study.

Public debate, based at least in part on further research, must be directed toward explicating the social service implications of identifying an asymptomatic child with laboratory evidence of cocaine exposure. In Massachusetts, there are no uniform guidelines or practices for health and social service professionals to follow when confronted

with documented cocaine exposure in an asymptomatic child. Further study on the physiologic and socioenvironmental effects of cocaine exposure in preschool children is needed to help direct rational and sound policy decisions on this issue.

Our findings suggest that significant numbers of infants and young children are being exposed to cocaine, and this exposure can occur in the absence of overt clinical signs. The clinical and public health implications of these findings, which are unknown at this time, are pressing topics in need of elucidation by subsequent surveillance and study.

This research was supported in part by Trustees of Health and Hospitals of the City of Boston Inc, BRSG 9057-09-00.

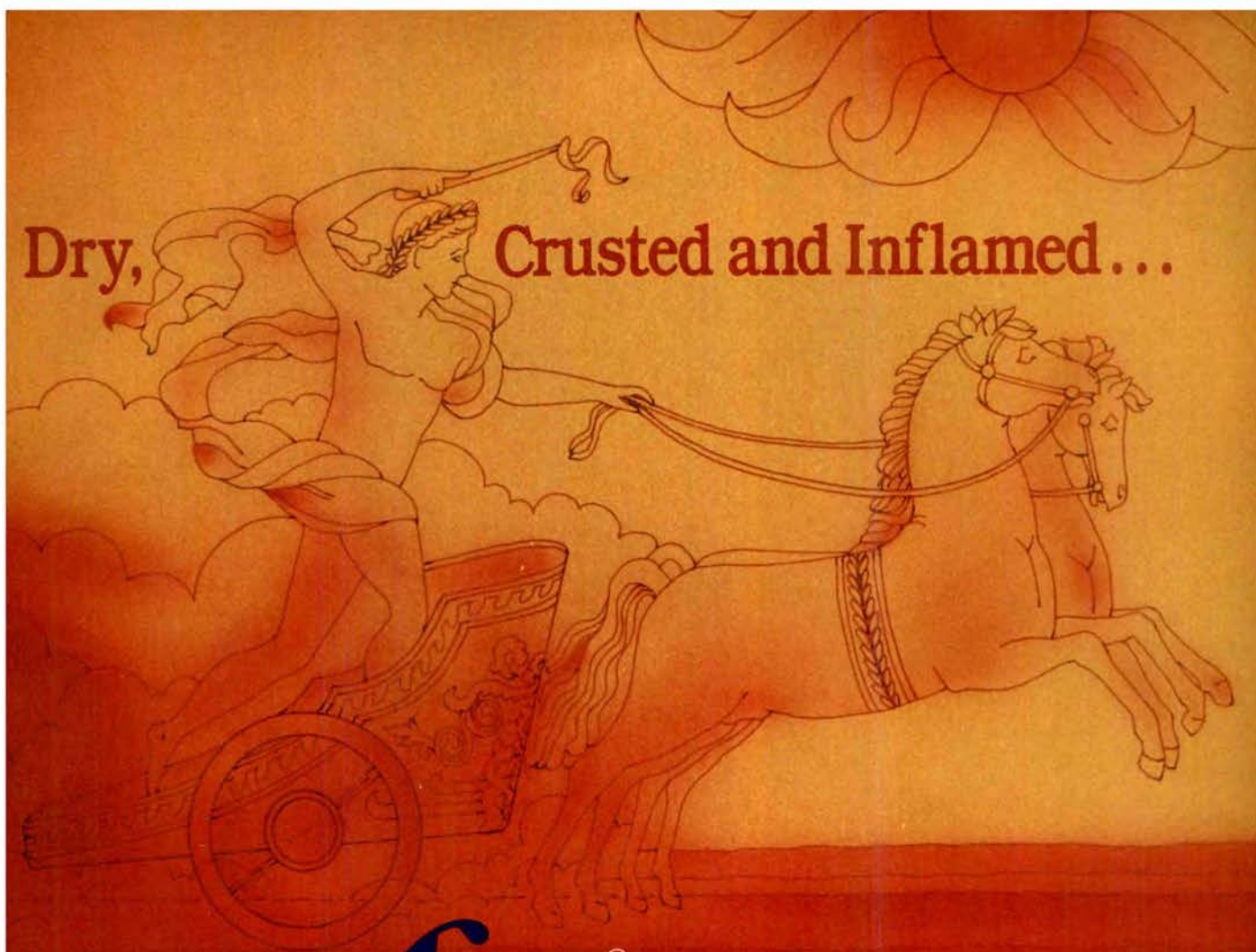
We thank the nursing staff of the Boston (Mass) City Hospital pediatric emergency department for their help in collecting urine samples and their continued efforts in our research projects. We also thank Howard Bauchner, MD, Marca Wilk, and Mary Grassley for their editorial assistance.

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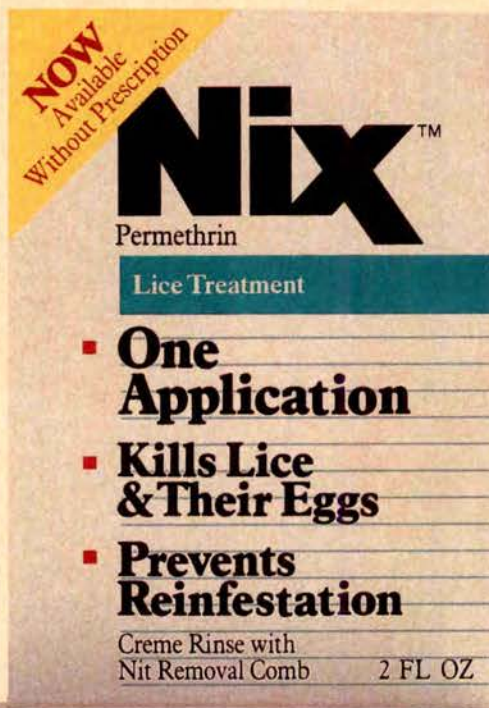
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Radiological Case of the Month

Kathlene S. Waller, MD, Jennifer Johnson, MD (Contributors); Beverly P. Wood, MD (Section Editor)

A previously healthy 15-year-old white boy presented with a 4-week history of cough and fever. At admission, he had a productive cough with thick, yellow sputum; intermittent daily temperatures of 38.5°C; night sweats; malaise; anorexia; and weight loss of approximately 4.5 kg. At the onset of illness, three siblings had had sore throats, but he had no history of a sore throat, recent travel, or exposure to animals. He had been smoking one pack of cigarettes per day for 2 years. Three months before admission, he was diagnosed as having mild asthma, and intermittently used inhaled epinephrine. He reported exposure to a friend who was diagnosed with tuberculosis the previous year and was receiving antituberculosis medications.

Vital signs on admission to the hospital were as follows: temperature, 39.4°C; heart rate, 120 beats per minute; respiratory rate, 32/min; and blood pressure, 110/60 mm Hg. Physical examination revealed a pale, thin, ill-appearing male in moderate respiratory distress with anterior and posterior cervical adenopathy, but no other enlarged

lymph nodes. Breath sounds were decreased and egophony was noted in the right upper and middle lobes. Expiratory wheezes were present bilaterally. There was no cyanosis or clubbing of the digits.

Chest roentgenograms were obtained (Figs 1 and 2). Initial laboratory results showed a white blood cell count of $25.9 \times 10^9/L$, with 0.73 segmented neutrophils, 0.08 band cells, 0.09 lymphocytes, 0.09 reactive lymphocytes, and 0.01 eosinophils. An arterial blood gas determination while the patient was breathing room air showed a pH of 7.49, P_{CO_2} of 34 mm Hg, and P_{O_2} of 52 mm Hg. A Gram's stain of sputum showed white blood cells; gram-positive cocci in pairs, chains, and clusters; and rare gram-negative bacilli. The original sputum culture yielded normal flora and moderate growth of β -hemolytic group C *Streptococcus*. No acid-fast bacilli were found. A purified protein derivative skin test using five tuberculin units was placed and was nonreactive in 48 hours. The mumps virus and *Candida* antigen were placed as controls and were also nonreactive. Antibiotic therapy was begun, but because the patient did not improve, he underwent bronchoscopy during his fourth day in the hospital. Much purulent material was recovered from the anterior, apical, and posterior segments of the right upper lobe. There was no obstructive lesion or inflammation in any other part of the bronchial tree.

Accepted for publication January 22, 1990.

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Figure 1.

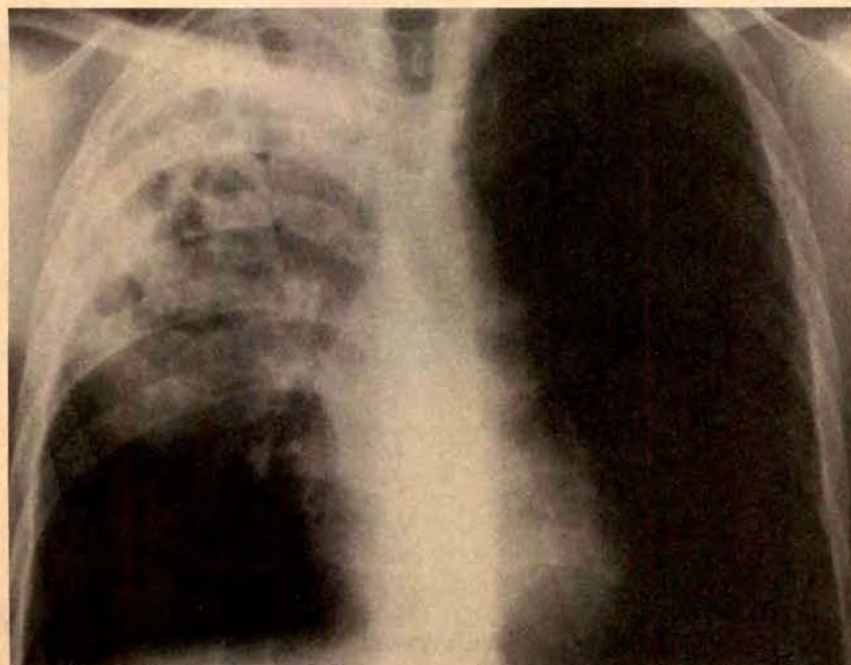
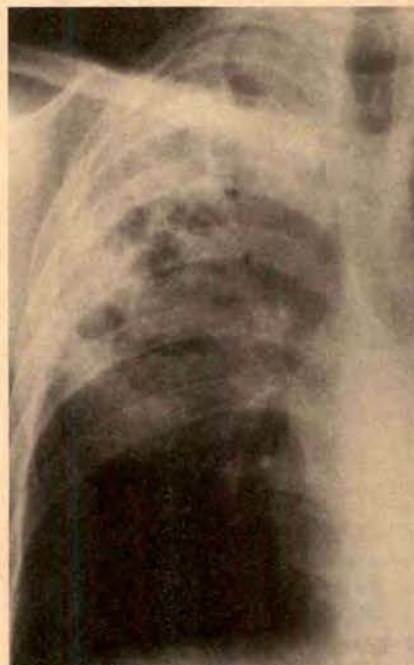


Figure 2.



Denouement and Discussion

Cavitary Pneumonia due to *Arcanobacterium hemolyticum*

Fig 1.—Posteroanterior chest roentgenogram shows consolidation of the right upper lobe and upper portions of the right middle and lower lobes.

Fig 2.—Coned view shows multiple cavitary areas with air-fluid levels and an air bronchogram in the consolidated lobes. Mediastinal adenopathy is present.

The chest roentgenogram taken on admission showed pulmonary consolidation and cavities with air-fluid levels, suggesting parenchymal abscesses or necrosis. Initial antibiotic therapy included treatment for gram-positive species, such as *Staphylococcus* species, and gram-negative species. The patient's history and roentgenogram were suggestive of tuberculosis, although a stain of the sputum showed no acid-fast bacilli, and the patient was anergic. Because the patient did not show clinical improvement, antituberculosis therapy was begun 6 days after admission to the hospital. Later that day, a rapidly growing organism, which had previously been reported as group C *Streptococcus*, was correctly identified as *Arcanobacterium hemolyticum*. The therapeutic regimen was changed to penicillin G and antituberculosis medications only. The boy showed marked improvement within 48 hours, with resolution of fever, decreased white blood cell count, and improved pulmonary aeration, as determined roentgenographically. Antituberculosis therapy was discontinued 10 days after admission to the hospital, and the patient was intravenously administered penicillin G for 4 weeks.

Cavitary pneumonia is an uncommon manifestation of pulmonary infection in children and young adults, but is associated with debilitating illness. Organisms causing lung abscesses include *Staphylococcus aureus*, *Streptococcus pyogenes*, *Klebsiella*, *Bacteroides*, *Mycobacterium tuberculosis*, and *Fusobacterium*.¹ This report illustrates the need also to consider *Arcanobacterium hemolyticum* as a pathogen in cavitary pneumonia.

Corynebacterium hemolyticum was recognized as a human pathogen in 1946, when it was isolated from infections of the nasopharynx and skin of American soldiers and natives of southwest Pacific islands.² This organism was considered a mutant of *Corynebacterium pyogenes*,^{3,4} and believed to be a purely human pathogen until it was isolated from a pneumonic sheep.⁵ This gram-positive, facultatively anaerobic organism appears initially as a slender, irregular bacillus, but with growth changes morphologically and appears as a small, irregular coccus. In 1982, the organism was removed from the *Corynebacterium* genus and reclassified under a new genus named *Arcanobacterium*.⁶

Arcanobacterium hemolyticum causes pharyngitis in young, healthy adults.⁷⁻¹¹ A scarlatiniform skin rash frequently accompanies the pharyngitis, which usually resolves in a few days, regardless of antibiotic therapy. Localized skin lesions, another common manifestation of *A hemolyticum* infection, are frequently ulcerative.^{2,8,9}

The organism also causes opportunistic infections in immunosuppressed patients. *Arcanobacterium hemolyticum* has caused vertebral osteomyelitis in a diabetic patient,¹² septicemia in an adolescent girl with infectious mononucleosis,¹³ and empyema in a woman with breast cancer.¹⁴

Serious infections in previously healthy hosts include peri-

tonsillar abscess,^{15,16} endocarditis,¹⁷ septicemia,¹⁸ brain abscess,¹⁹ and bacteremia,²⁰ but this is the first reported case of cavitary pneumonia. Because of the rarity of serious infection in immunologically normal hosts, this patient was evaluated for immunodeficiency. Results of all tests were normal, except B-cell subsets had decreased slightly both 10 days and 1 month after admission to the hospital.

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Picture of the Month

Jeffrey R. Schneider, MD, Howard Fischer, MD (Contributors); Murray Feingold, MD (Section Editor)

Figure 1.



Figure 2.

Figure 3.



Accepted for publication August 15, 1990.

Contributed from the Department of Pediatrics, Children's Hospital of Michigan, and the School of Medicine, Wayne State University, Detroit, Mich.

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Denouement and Discussion

Acrodermatitis Enteropathica

Fig 1.—Erosive lesions around eyes and mouth.

Figs 2 and 3.—Emaciated infant with rash surrounding body orifices and a symmetric distribution of lesions on the extremities.

Manifestations

Acrodermatitis enteropathica is a rare hereditary disorder affecting zinc metabolism that is characterized by dermatitis, alopecia, gastrointestinal disturbances, eye infections, and growth failure. Poor wound healing and impaired cellular immunity have also been described as manifestations of this disorder. Acrodermatitis enteropathica was so named because of the acral distribution of skin lesions and the severe gastrointestinal disturbances it causes.

The classic triad of dermatitis, diarrhea, and alopecia is often seen in newborns and in early infancy. Symptoms may appear within 2 weeks of weaning from breast milk to cow's milk. Infants with acrodermatitis enteropathica typically are listless and anorexic and many have a wasted appearance with little subcutaneous fat. Skin manifestations begin with small, moist, erythematous lesions localized around body orifices (mouth, nose, ears, eyes, and perineum) and progress to a vesicobullous eruption with erosions. Symmetrically distributed lesions occur on the buttocks, the extensor surfaces of major joints, and the fingers and toes.

Later, the vesicobullous eruptions become dry, hyperkeratotic, and psoriasisform in appearance. Diarrhea in this disorder is severe, with steatorrhea, lactose intolerance, and progressive malabsorption. Eye manifestations include blepharitis, conjunctivitis, photophobia, and corneal opacities. Secondary monilial or bacterial skin infec-

tions occur frequently. The infections and severe malnutrition may lead to marasmus and death within 1 to 3 years in the untreated patient.

The diagnosis is established by the clinical findings and laboratory evidence of zinc deficiency. Plasma zinc levels are often below $7.7 \mu\text{mol/L}$ (normal levels are 10.7 to $16.8 \mu\text{mol/L}$). Other useful laboratory findings include deficiency of certain zinc-dependent enzymes, such as alkaline phosphatase, and marked alterations of the fatty acid profile of plasma lipids. Skin biopsy is not diagnostic of this disorder.

Genetics

The mode of inheritance is considered to be autosomal recessive. The basic defect is presumed to be related to gastrointestinal malabsorption of zinc, but the exact mechanism is not yet understood.

Treatment

The treatment of choice is oral administration of zinc, usually in the sulfate or gluconate form. It is usually well tolerated, safe, inexpensive, effective, and expedient in rapidly reversing the manifestations of the disease. For many years, acrodermatitis enteropathica was treated empirically with iodoquinol and breast milk, a now outdated treatment.

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Late Cholangitis After Successful Surgical Repair of Biliary Atresia

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• Bacterial cholangitis is a frequent complication of successful surgical repair of biliary atresia, occurring in 93% of patients before the age of 1 year, but thought to be rare after 2 years of age. Among 76 children free of jaundice more than 5 years after operation, four presented with late cholangitis (7 to 13.5 years old), consisting of fever, jaundice, and abdominal pain with biochemical features of an inflammatory process and cholestasis. Liver biopsy specimens consistently demonstrated histological features of cholangitis, growth of microorganisms, or both. Cholangitis subsided spontaneously in one patient or in response to intravenous administration of antibiotics. Cholangiography consistently demonstrated biliary abnormalities but no definite obstruction to the bilioenteric anastomosis. All the children had good hepatic function 3 weeks to 4 years after the episode of cholangitis. These results suggest that cholangitis may occur several years after surgery but does not seem to alter prognosis.

(AJDC. 1991;145:213-215)

Bacterial cholangitis is a frequent complication of surgery for biliary atresia, occurring in about 30% of patients.¹ This frequency increases after successful hepatoportoenterostomy to above 50%.¹⁻³ It occurs most often within the first months after surgery, 93% of patients being observed before the age of 1 year.¹ Early cholangitis may worsen the prognosis, with increase in mortality, secondary failure of restoration of bile flow, and possible exacerbation of portal hypertension.^{1,3-8} However, the frequency of cholangitis decreases with age and is considered rare after 2 years.¹ Indeed, only a few reports briefly note the possibility of late occurrence of cholangitis.^{3,7,9-14}

We report the clinicopathological histories of four children operated on successfully for biliary atresia who presented with acute cholangitis at the ages of 7 to 13 years.

Accepted for publication September 5, 1990.

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PATIENT REPORTS

Between 1970 and 1982, 207 children who were operated on for biliary atresia were followed up at Bicêtre Hospital, Le Kremlin-Bicêtre, France. Seventy-six patients became free of jaundice. Among these, four children presented with late cholangitis, defined as follows: occurrence more than 2 years after surgery; exclusion of extrahepatic causes for fever; and a liver biopsy specimen either demonstrating histopathological signs of cholangitis or yielding several organisms on bacterial culture. Their histories follow.

PATIENT 1.—This girl was operated on at the age of 41 days for biliary atresia of the hepatic ducts. A hepatic portocholecystostomy was placed initially because of a patent gallbladder and choledochus. Postoperative choleperitonitis made it necessary to perform a hepatic portoenterostomy with external jejunostomy at the age of 67 days. Bile excretion was observed on the 11th postoperative day, and she became free of jaundice. Acute bacterial cholangitis developed 2 months after the last operation, which subsided in response to intravenous antibiotics. One year later, ultrasonography showed a cystic cavity 2 cm in diameter in the left lobe of the liver. Percutaneous transhepatic cholangiography was performed at the age of 2 years and showed the cystic cavity communicating with a patent portoenterostomy. The intrahepatic bile ducts were irregular. The external jejunostomy was closed at the age of 2.5 years. She remained free of jaundice for several years, with normal liver function test results. The liver was enlarged and firm and displayed histological features of micronodular cirrhosis. Ultrasonography and fibroscopy showed no portal hypertension. Repeated ultrasonography at the age of 8 years did not show any cyst or bile duct dilatation.

At the age of 8.5 years, fever, jaundice with clay-colored stools, abdominal pain, and vomiting developed, with abnormal laboratory findings (Table). Liver histological study (needle biopsy specimen) showed cholangitis with a polymorphonuclear cell infiltration around and inside the bile ducts. Liver and blood cultures remained negative. Intravenous cefotaxime sodium and amikacin sulfate were given for 3 weeks. Fever disappeared within 2 days, and jaundice disappeared gradually. Three months later, liver function test results were normal (Table).

PATIENT 2.—This boy was operated on at the age of 56 days for biliary atresia. A biliary cystic cavity at the porta hepatis was communicating with the intrahepatic bile ducts. A Roux-en-Y jejunal anastomosis to the cyst was performed. Normal-colored stools were seen 10 days later, and the boy became free of jaundice. Acute bacterial cholangitis developed 7 months later and was successfully treated by intravenous administration of antibiotics. He remained free of jaundice for several years, with normal laboratory liver function test results. The liver was not enlarged but showed histological features of moderate portal

Clinical and Laboratory Features in Four Cases of Late Cholangitis*

Signs	On Admission	On Follow-up	
		1-4 wk Later	4 mo to 4 y Later
Clinical features			
Fever	4/4	0/4	0/4
Jaundice	4/4	0/4	0/4
Abdominal pain	4/4	0/4	0/4
Abnormal laboratory features			
WBC count	1/4	0/4	0/4
ESR	3/4	0/3	0/3
CRP	2/2	0/2	0/2
Bilirubin	4/4	0/4	0/4
γ -Glutamyltransferase	4/4	4/4	1/4†
Alkaline phosphatase	3/4	3/4	1/4†
ALT	4/4	4/4	1/4†

*WBC indicates white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; and ALT, alanine aminotransferase.

†Patient 3.

fibrosis (needle biopsy specimen). There was no ultrasonographic or endoscopic evidence of portal hypertension. Ultrasonography did not show any cavity or dilatation of the bile ducts.

At the age of 8.5 years, fever, jaundice, and abdominal pain developed, all suggestive of cholangitis, but liver histological study and cultures were negative. Percutaneous transhepatic cholangiography showed abnormal intrahepatic bile ducts with stenosis and dilatations but an early opacification of the gut. Antibiotics were administered and fever and jaundice cleared.

At the age of 13.5 years, he again presented with fever, jaundice, and abdominal pain, with abnormal laboratory findings (Table). Liver histological study showed cholangitis with a polymorphonuclear cell infiltrate around and inside the bile ducts (Fig 1). Liver and blood cultures were negative. Symptoms resolved spontaneously within a few days. Repeated percutaneous transhepatic cholangiography demonstrated the same abnormalities of the intrahepatic bile ducts with rapid opacification of the gut (Fig 2).

At the age of 15.5 years, he again presented with the same symptoms. Liver histological study and culture were negative. Antibiotics were given for three weeks, and clinical and biological features resolved. He is 17 years old and has normal growth, no jaundice, no liver or spleen enlargement, normal liver function test results, and no signs of portal hypertension.

PATIENT 3.—This girl was operated on at the age of 112 days for biliary atresia, and a hepatic portoenterostomy with external jejunostomy was performed. She had normal-colored stools 1 month later, and her bilirubin level was normal 2 months later. The external jejunostomy was closed at the age of 2 years.

She remained free of jaundice for several years but with persisting biochemical signs of cholestasis (total bilirubin, 16 μ mol/L; alkaline phosphatase, 490 U/L; γ -glutamyltransferase, 155 U/L). The liver was enlarged and firm with moderate splenomegaly, and a liver needle biopsy specimen showed histological features of micronodular cirrhosis. There were no endoscopic or ultrasonographic signs of portal hypertension. Ultrasonography did not show any intrahepatic bile duct abnormalities.

At the age of 7 years, she had fever, jaundice, and abdominal pain with abnormal laboratory findings (Table). *Escherichia coli* and *Enterococcus* species were isolated by cultures of the liver obtained by needle biopsy. The liver had moderate polymorphonuclear cell infiltrate around the bile ducts but none within the ducts themselves. Intravenous trimethoprim-sulfamethoxazole and netilmicin sulfate were given for 3 weeks, and clinical and biological features resolved (Table). An attempt at percutaneous transhepatic cholangiography failed. She is 9.5 years old and has normal growth, no jaundice, but persistently increased γ -gluta-



Fig 1.—Detail of a fibrous portal area showing polymorphonuclear leukocytes inside and around a bile duct (hematein-eosin, $\times 170$).



Fig 2.—Percutaneous transhepatic cholangiography (patient 2) showing irregularly dilated intrahepatic ducts (higher arrow) and a patent anastomosis (lower arrow).

myltransferase and alkaline phosphatase levels. There were no esophageal varices, but at ultrasonography the lesser omentum was enlarged.

PATIENT 4.—This boy was operated on for biliary atresia at the age of 57 days, and a hepatic portoenterostomy with external jejunostomy was performed. He had normal-colored stools in a few days and normal bilirubin values 2 months later.

Two episodes of acute cholangitis occurred 2.5 and 4.5 months after surgery. He then remained free of jaundice. Percutaneous transhepatic cholangiography performed at 1 year of age demonstrated narrowed and irregular intrahepatic bile ducts with rapid opacification of the gut. The external jejunostomy was closed at the age of 2 years. He was healthy, with normal laboratory liver function test results. The liver and spleen were not enlarged, but liver histological study (needle biopsy specimen) showed portal fibrosis. There was no sign of portal hypertension. At the age of 7 years he had fever, jaundice, and abdominal pain with abnormal laboratory findings (Table). Liver histological

study showed cholangitis with a polymorphonuclear cell infiltrate around and inside the bile ducts. Cultures of blood and a liver biopsy specimen were negative. Ultrasonography showed no cavity or bile duct dilatation. Intravenous trimethoprim-sulfamethoxazole and amikacin were given for 3 weeks. Fever disappeared in 3 days, and he was anicteric on discharge from the hospital (Table). Four months later, he was healthy, with no jaundice or signs of portal hypertension, and had normal growth.

COMMENT

Late cholangitis is a rare complication of surgery for biliary atresia not mentioned in several large series with more than 5 years of follow-up.^{4,7,8,15} Lilly and Hitch¹² report five cases of cholangitis occurring 1 to 2 years after operation. Nevertheless, we were only able to find five patients with cholangitis presenting after 2 years.^{9-11,14,16} Three of them occurred after hepatoportoenterostomy,^{9,14,16} one after choledochoduodenostomy,¹¹ and one after hepaticoduodenostomy.¹⁰ Late cholangitis occurred at the age of 2.5 to 16 years. Clinical features, when described, consisted of fever, jaundice, and abdominal pain, as in the patients described here. Early cholangitis was absent in two children,^{10,11} as in our patient 3. When there was obstruction of the bilioenteric conduit^{10,12} or severe intestinal obstruction,^{14,16} cholangitis was refractory to treatment or relapsed. However, no definite mechanical obstruction to the bilioenteric system was found in the report of Werlin et al,⁹ as well as in our four patients. However, when cholangiograms were performed, abnormalities of intrahepatic bile ducts, ie, narrow or dilated ducts, draining and nondraining cysts, were always seen,^{9,11,14} as in our report.

From our patient reports, the main characteristics of late cholangitis after successful surgery for biliary atresia may be summarized as follows: (1) Late cholangitis may occur several years after operation, even if there was no previous episode of early cholangitis. (2) It occurs in children with a healthy appearance; normal liver function test results (three cases) despite liver fibrosis (two) or cirrhosis (two); no or mild portal hypertension (one). (3) Late cholangitis was only seen in children with good bile flow, supporting the concept of a direct ascending cholangitis from intestinal bacteria. Biliary stasis secondary to narrow intrahepatic bile ducts and tiny bilioenteric anastomoses may contribute to cholangitis. Nevertheless, there was no definite mechanical obstruction to the bilioenteric system. The partial obstruction of intrahepatic bile ducts may resolve spontaneously. (4) Features of cholangitis resolve rapidly with use of intravenous antibiotics or spontaneously, as in one of these cases. Late cholangitis does not seem to alter the evolution of the liver condition but may relapse.^{14,17} However, Kasai et al^{14,16} describe a patient operated on successfully for biliary atresia who died at the age of 29 years after several episodes of late cholangitis. In a few patients, late cholangitis refractory to antibiotic therapy may require liver transplantation.

From the data reported herein, we suggest that children with features of late cholangitis after successful surgery for biliary atresia first have blood cultures taken and be observed for 3 to 4 days, clinical condition permitting. If fever continues and blood cultures are negative, liver needle biopsy should be performed and a 3-week regimen of intravenous antibiotics started. If fever subsides spontaneously, careful follow-up is necessary until all biochemical abnormalities of the liver function tests and inflammatory signs return completely to normal. This approach should prevent unnecessary treatment of a cholangitic episode that can resolve spontaneously; however, antibiotic treat-

ment and follow-up could prevent an ongoing inflammatory process of the intrahepatic bile ducts, with the subsequent risk of complete obstruction, cyst formation, or refractory cholangitis. Should cholangitis recur, a percutaneous cholangiography should be performed in search of obstruction of the bilioenteric anastomosis.^{9,18}

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Revaccination: Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use with Other Vaccines: Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) (using separate sites and syringes), or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine or the diluent.

WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: General: As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with *Haemophilus b* polysaccharide vaccine and another *Haemophilus b* conjugate vaccine, cases of *Haemophilus b* disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of *Haemophilus b* polysaccharide vaccines and another *Haemophilus b* conjugate vaccine has been associated with the following additional adverse effects: early onset of *Haemophilus b* disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

Age (Months)	Reaction	Dose 1			Dose 2				
		Number of Subjects Evaluated	6 hr	24	48	Number of Subjects Evaluated	6 hr.	24	48
2-14*	Fever >38.3°C (101°F)								
	Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/ Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F)								
	Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/ Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against *Haemophilus b* disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (*Haemophilus b* Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group (see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792—PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797—PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

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Factors Affecting Outcome in Meningococcal Infections

Louis J. Tesoro, MD, Steven M. Selbst, MD

● A prognostic score for evaluating meningococcal infections in patients consists of the following five features that indicate a poor prognosis: onset of petechiae within 12 hours of presentation; shock; normal or low peripheral leukocyte count; normal or low erythrocyte sedimentation rate; and absence of meningitis. Based on our experience and some published data, we suspected that the score may no longer be reliable. We reviewed the charts of 73 children with meningococcal infection from December 19, 1979 to December 19, 1987 and applied the prognostic score mentioned previously. Our findings indicate that although a low score is generally associated with a good outcome, a higher score is less predictive of poor outcome than previously suggested. A rash with petechiae or purpura, the presence of shock, and a normal or low peripheral leukocyte count continue to be predictors of poor outcome. Erythrocyte sedimentation rate was not evaluated owing to a limited amount of data. The absence of meningitis did not correlate with a worse outcome in our patients. Most patients who died had evidence of meningeal involvement at the time of presentation. Instead, altered mental status at presentation, particularly obtundation or coma, was an ominous sign. We conclude that absence of meningitis is not a good predictor of outcome, as was previously thought. Altered mental status at the time of presentation may prove to be a stronger indicator of poor outcome.

(AJDC. 1991;145:218-220)

A review of 63 cases of meningococcal disease in 1966 by Stiehm and Damrosch¹ identified five factors that were highly correlated with bad outcome. They were onset of petechiae within 12 hours prior to hospital admission, shock, normal or low leukocyte (WBC) count, normal or low erythrocyte sedimentation rate, and absence of meningitis. The presence of three or more of these features indicated a poor prognosis. Niklasson et al² found similar results in Sweden during the 1960s. We reviewed 73 cases of meningococcal infection in patients seen from December 1979 to December 1987 to reexamine the prognostic factors noted by Stiehm and Damrosch and others.

PATIENTS, MATERIALS, AND METHODS

Patients were identified for the study in two ways. Microbiology laboratory records were reviewed from December 19, 1979, to December 19, 1987, and all patients with cultures of cerebrospinal

fluid (CSF), blood, or joint fluid positive for meningococcal infections were included. Also, medical record hospital discharge code books from the same period were reviewed, and all patient charts with hospital discharge codes indicating meningococcal disease were examined. Seventy-three patients were included in the study. Of those, 68 had positive CSF or blood cultures for meningococcus, two had positive CSF latex agglutination and a typical course of meningococcal disease, two had a typical course of meningococcal disease with gram-negative diplococci in the CSF, and one had a typical course of meningococcal disease plus a positive joint culture. One patient with a positive blood culture was excluded because he was transferred to another hospital and was unavailable for follow-up. Multiple factors were analyzed to see if they were associated with mortality.

Data were analyzed using the Statistical Package for the Social Sciences. Unless otherwise indicated, $P < .05$ is considered significant.

RESULTS

Seven deaths occurred among 73 patients for a fatality rate of 10%. This is not significantly different from the 19% fatality rate in the Stiehm-Damrosch¹ study. Although 42 (57%) of the cases occurred between December and April, there was no month or year with a higher mortality rate. The patients were usually male (79%) and white 46 (63%); fatality was not related to gender or race. The ages of patients ranged from 1 month to 15 years. Two (5%) of 40 who were younger than 2 years died, whereas five (15%) of 33 patients between the ages of 2 and 15 years died. The difference does not vary significantly from the expected outcome. These results are similar to those reported by other authors.²⁻⁵

The relationship between the five significant Stiehm-Damrosch¹ variables and fatality was examined for our 73 patients. First we compared the absence of meningitis with fatality (Table 1). We used the definition established by Stiehm and Damrosch for meningococcal meningitis ($>20 \times 10^6/L$ WBCs in CSF with positive CSF culture or with negative culture if pretreated with antibiotics) and meningococcemia (positive blood culture or petechial rash with negative blood culture if pretreated). Our table excludes five patients who did not have a lumbar puncture performed or five patients who did not fit the Stiehm-Damrosch definitions. Fatality was not significantly related to the presence or absence of meningitis. One (4%) of 26 patients with meningitis only died compared with one (5%) of 20 with both meningitis and meningococcemia and two (12%) of 17 with meningococcemia only.

However, this definition of meningitis excluded some patients with positive CSF cultures just because they had less than $20 \times 10^6/L$ WBCs, as well as those with significant pleocytosis greater than $20 \times 10^6/L$ WBCs in CSF, with pos-

Accepted for publication July 8, 1990.

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Table 1.—Relationship of Death From Meningococcemia With the Presence of Meningitis (as Defined by Stiehm and Damrosch¹)

Illness Present	n	Died	%	P
Meningitis only (positive CSF culture, negative blood culture, CSF pleocytosis)	26	1	4	>.05
Meningitis and meningococcemia (positive CSF culture, positive blood culture, CSF pleocytosis)	20	1	5	>.05
Meningococcemia only (negative CSF culture, positive blood culture, no CSF pleocytosis)	17*	2	12	>.05

*Includes eight patients with positive cerebrospinal fluid (CSF) cultures but less than $20 \times 10^6/L$ leukocytes (WBCs) in the CSF; and one patient with negative CSF cultures but more than $20 \times 10^6/L$ WBCs. These patients did not have meningitis by the Stiehm-Damrosch strict criteria.

Table 2.—Relationship of Death From Meningococcemia and Presence of Cerebrospinal Fluid (CSF) Pleocytosis ($>20 \times 10^6/L$ White Blood Cells)*

	Pleocytosis	
	Present	Absent
n	48	18
Died	4	2
%	8	11
P	...	>.05

*Excluded are five patients who did not have lumbar puncture and two patients with unknown CSF cell counts.

itive blood culture and negative CSF culture. No significant difference in fatality rate (Table 2) was noted when those with pleocytosis greater than $20 \times 10^6/L$ WBCs were compared with those without pleocytosis. Next, we looked at meningeal involvement, including the presence of a positive CSF culture, a positive CSF Gram stain, a positive CSF latex agglutination, or CSF pleocytosis. Patients with these findings were evaluated for fatality (Table 3). Of the seven patients who died, all had evidence of meningeal involvement. Eight patients with normal CSF survived. Five additional patients (not listed) who did not require lumbar punctures as part of their evaluation also survived. Thus, our results do not support the notion that absence of meningitis results in increased mortality.

Next, we evaluated the relationship between death and the presence of a petechial or purpuric rash within 12 hours prior to presentation. Unlike Stiehm and Damrosch,¹ we did not find a relationship between time of onset of the rash and death, probably because so few presented with such a rash after 12 hours. No patients (none of eight patients) with petechiae/purpura noted more than 12 hours into the illness died, but seven of 36 with early onset of this rash (<12 hours) died. This was not significantly different. However, the presence of this nonblanching rash on initial physical examination was important. Seven (19%) of 37 with petechiae, purpura, or purpura fulminans died, whereas none of 36 died if they had no petechiae or purpura ($P<.01$) (Table 4).

Next, we compared the relationship between death and the initial peripheral WBC count (Table 5). There is a high mortality rate associated with a WBC count less than $5 \times 10^9/L$, but no deaths are associated with a WBC count between 5.1 and $15 \times 10^9/L$. Only nine erythrocyte sedi-

Table 3.—Relationship of Death From Meningococcemia With Any Meningeal Involvement*

	Meningeal Involvement	
	Present	Absent
n	60	8
Died	7	0
%	12	0
P	<.05	...

*Positive cerebrospinal fluid (CSF) culture or Gram stain, positive CSF latex agglutination, or CSF pleocytosis.

Table 4.—Relationship of Death From Meningococcemia and the Presence of Petechiae/Purpura

	Petechiae/Purpura	No Rash
n	37	36
Died	7	0
%	19	0
P	...	<.01

Table 5.—Relationship of Death From Meningococcemia and Peripheral Leukocytes (WBCs)

WBC, $\times 10^9/L$	n	Died	%	P
≤ 5	12	5	42	<.01
5-10	16	0	0	...
10-15	17	0	0	...
>15	27	2	7	...

mentation rates were recorded; these were not analyzed.

Shock was present in 19 patients at time of presentation, and six (32%) of these patients died (Table 6). Only one (2%) of 53 patients who did not present with shock died ($P<.01$). This death was related to rapidly progressive cerebral edema. In 12 patients, shock persisted despite aggressive fluid resuscitation and pressor therapy was started. Six (50%) of 12 patients who received pressors died, compared with only one (2%) of 61 patients who did not require pressors.

We compared several clinical factors and laboratory values with outcome. Several factors are not related to death from meningococcemia, including the following: history of previous severe infection; duration of illness prior to presentation; duration of rash prior to presentation; history of fever; presence of bulging fontanelle; joint involvement; serum sodium concentration; hemoglobin value; differential cell count (peripheral blood); CSF WBC count, differential cell count, red blood cell count, protein concentration, glucose concentration, or Gram's stain (initial); blood culture results; absence of meningitis; and choice of antibiotic. Several factors that are related to death from meningococcemia ($P<.01$) are as follows: presentation to another hospital prior to transfer; change in mental status; coma; shock; nonblanching rash; purpura fulminans; peripheral WBC count; elevated serum creatinine value; prolonged prothrombin time or partial thromboplastin time; severe disseminated intravascular coagulation; need for intubation; and need for pressors. Presenting to another hospital prior to transfer to our hospital was one factor associated with higher mortality. Those who required transfer to our center may have been more ill to begin with

Table 6.—Relationship of Death From Meningococcemia to Presence of Shock

	Shock	
	Absent	Present
n	53	19
Died	1	6
%	2	32
P	...	<.01

or may have had a delay in definitive treatment. Of those factors studied, however, we found that a change in mental status is most closely associated with mortality in meningococcal infection. None of 56 patients who had normal mental status or only irritability or lethargy died, whereas seven (41%) of 17 of the patients who were obtunded or comatose at the time of presentation died ($P<.01$) (Table 7). Five (83%) of six patients who presented in coma died.

We applied the Stiehm-Damrosch¹ factors associated with poor outcome (excluding erythrocyte sedimentation rate) to our patients (Table 8). Only one (2%) of 50 patients with a score of 1 or 0 died, whereas six (26%) of 23 with scores greater than 1 died. Five (55%) of nine patients with the highest scores survived.

COMMENT

We examined each of the Stiehm-Damrosch¹ factors associated with poor prognosis in meningococcal infections (except erythrocyte sedimentation rates). We found that the absence of meningitis, as defined by Stiehm and Damrosch or defined by the absence of CSF pleocytosis, or the absence of meningeal involvement of any kind, are unimportant predictors of mortality. The reason for the discrepancy between the findings of Stiehm and Damrosch and ours regarding this issue is unclear.

Although peripheral WBC count continues to be associated with poor outcome, we discovered that a suppressed WBC count rather than a normal WBC count in the face of meningococcal infection is significant. Shock remains a significant marker for mortality. Furthermore, we found that the presence of nonblanching rash is a sensitive indicator of fatality. We could not determine if the early onset of this rash is important.

Despite some shortcomings, the Stiehm-Damrosch¹ score still identifies patients with a good outcome. It is less reliable for poor outcome. This could be due to the fact that in the last three decades, we have become better able to treat the severely ill child with meningococcal infection. Five (55%) of nine critically ill patients, those with the highest Stiehm-Damrosch scores, survived. All of these were treated aggressively with intensive care, intubation, pressors, and steroids. We suggest that this treatment altered the outcome of these patients and may have rendered the Stiehm-Damrosch score less useful in predicting poor outcome than when it was developed 30 years ago.

Inspired by these results, yet challenged by the fact that we could not demonstrate a reduced mortality rate overall, we looked for other factors that predict poor outcome. Of those we examined, we discovered that altered mental status at the time of presentation, particularly coma, was associated with a grave prognosis. We suggest that the presence of altered mental status, like the presence of shock, low peripheral WBC count, and nonblanching rash, become a "red flag" to the practitioner of the likelihood of poor prognosis. Table 9 compares the Stiehm-Damrosch¹

Table 7.—Relationship of Death From Meningococcemia to Mental Status

	Mental Status	
	Normal, Irritable, or Lethargic	Obtunded, Coma
n	56	17
Died	0	7
%	0	41
P	...	<.01

Table 8.—Stiehm-Damrosch¹ Prognostic Score Applied to Our Patients*

Prognostic Score	n	Died	%
0	24	0	0
1	26	1	4
2	14	2	14
3	7	4	57
4	2	0	0

*One point each for normal or low peripheral leukocyte count, shock, onset of petechiae within 12 hours of presentation, and absence of meningitis. Erythrocyte sedimentation rate was not evaluated.

Table 9.—Comparison of Stiehm-Damrosch¹ Criteria to New Factors Associated With Poor Outcome

Stiehm-Damrosch	Proposed New Factors
Shock	Shock
Normal or low WBC*	Low WBC*
Rash within 12 h	Rash
Absent meningitis	Altered mental status
Low erythrocyte sedimentation rate	

*WBC indicates white blood cell count.

criteria with the proposed criteria found useful herein. Of course, these factors should be tested prospectively on other patients to see if they reliably predict fatality.

CONCLUSION

Presumably because of our improved ability to treat patients with meningococcal infection, prognostic factors developed 30 years ago may no longer be as helpful in predicting outcome. The absence of meningitis does not correlate with a poor outcome. Different criteria, including changes in mental status, shock, presence of nonblanching rash, and low peripheral WBC count may be better predictors of those patients at greatest risk for death from meningococcemia.

Pat Parkinson provided assistance with preparation of the manuscript.

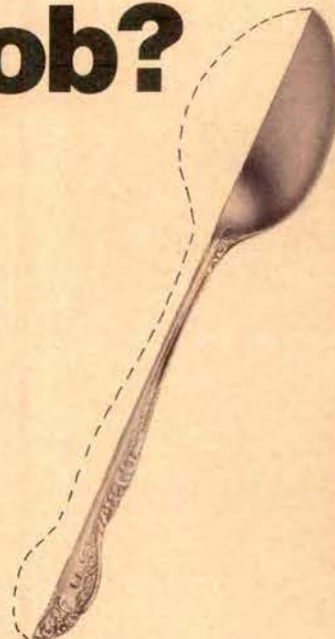
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Nursing Mothers— Do not administer to a nursing woman.

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OVERDOSAGE: No reports of any serious problems.

DOSAGE AND ADMINISTRATION: Adults: 1 to 2 teaspoonfuls every 4 hours. Children: 1/2 to 1 teaspoonful every 4 hours.

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Antibody Responses to Four *Haemophilus influenzae* Type b Conjugate Vaccines

H. Käyhty, PhD; J. Eskola, MD; H. Peltola, MD; P-R. Rönöberg, RN; E. Kela, RN; V. Karanko, RN; L. Saarinen, MSc

• Serum antibody responses to four *Haemophilus influenzae* type b capsular polysaccharide-protein conjugate vaccines (PRP-D, HbOC, C7p, and PRP-T) were studied and compared in 175 infants, 85 adults, and 140 2-year-old children. Antibodies to the H influenzae type b polysaccharide vaccines were determined with a Farr-type radioimmunoassay. The infants received two doses of vaccine at the ages of 4 and 6 months. After the first dose of vaccine, the geometric mean antibody concentration measured at the age of 6 months was 0.09 to 0.10 mg/L, only marginally higher than that measured before immunization in all infants who had received PRP-D, HbOC, or C7p but increased to 0.82 mg/L in those who had received PRP-T. One month after the second dose, the geometric mean antibody concentration was increased in all vaccine groups. No significant differences were noted between recipients of HbOC, C7p, or PRP-T (geometric mean antibody concentrations, 4.32, 3.10, and 6.10 mg/L, respectively), whereas the PRP-D recipients had a significantly lower geometric mean antibody concentration (0.63 mg/L). In contrast, PRP-D, HbOC, C7p, and PRP-T were all highly immunogenic in adults, with no differences noted among them. The 2-year-old children also responded to one dose of these vaccines with a high antibody concentration.

(AJDC. 1991;145:223-227)

Haemophilus influenzae type b (Hib) is the most common cause of bacteremic infections in infants and young children.^{1,2} Although mortality due to these diseases has decreased to less than 5% as a result of efficient treatment, the occurrence of severe sequelae in survivors remains high.³⁻⁵ A vaccine that could prevent this morbidity would therefore be welcome.

Early in this century, covalent coupling of the capsular polysaccharide (PS) of *Pneumococcus* to a protein carrier was described.^{6,7} Many variations of such conjugate vaccines are possible depending on the protein carrier, the length of the PS chain, the linker, and the coupling procedure. Several groups and manufacturers have produced vaccines against Hib that incorporate some of these variations. Thus, PRP-D is composed of PS coupled to diphtheria toxoid via an adipic acid linker, as described originally by Schneerson et al⁸ and

Gordon.⁹ A related preparation (PRP-T) that employs tetanus toxoid instead of diphtheria toxoid was originally described by Chu et al.¹⁰ HbOC contains oligosaccharides (OSs) directly coupled by reductive amination to a nontoxic variant diphtheria toxin, CRM197; the OSs are activated biterminally so that they can bind to the protein at both ends.¹¹ Porter Anderson (University of Rochester [NY]) has prepared a series of vaccines, eg, C7p, in which uniterminally activated OSs are coupled to the protein (either diphtheria toxoid or CRM197) at one end.¹² In PRP-OMP, PS is coupled by a bigeneric linker to an outer membrane protein-complex isolated from *Neisseria meningitidis* group B, type 2a.¹³

All of these vaccines have been shown to be immunogenic in human infants.^{11,14-18} A comparison of the vaccines is difficult based on the published data, as there are no standardized assays for anti-Hib PS and results from different laboratories may not be directly comparable.¹⁹⁻²¹ Separate studies, however, suggest differences in immunogenicity. Furthermore, the extent to which the immunogenicity of the vaccines in adults or older children would predict immunogenicity in infants is unclear.

To consolidate the data base, we have compared, under similar conditions, the immunogenicity and reactogenicity of four Hib conjugate vaccines in infants immunized at 4 and 6 months of age, adults, and 2-year-old children; some of the data have been previously published,^{22,23} but they are presented herein together with the new data to facilitate comparison.

PATIENTS AND METHODS

Vaccines, Vaccinees, and the Vaccination Schedules

The Hib vaccines used are listed in Table 1. The vaccination protocol was approved by the Ethical Committee of the National Public Health Institute, Helsinki, Finland. Informed consent was obtained from the adult vaccinees or from the parents of children and infants.

Healthy infants were recruited at the age of 3 months from the child health centers of two towns: Joensuu and Kerava. Seventy-two infants received PRP-D, 46 received HbOC, 32 received C7p, and 25 received PRP-T at the ages of 4 and 6 months. At the age of 4 months, they also received their second dose of diphtheria-pertussis-tetanus vaccine (National Public Health Institute); at the age of 6 months, they received their first dose of poliomyelitis vaccine (inactivated poliovirus vaccine; RIVM, Bilthoven, the Netherlands). The Hib vaccines were given intramuscularly into the right buttock, and the diphtheria-pertussis-tetanus and inactivated poliovirus vaccines were administered intramuscularly into the left buttock.

Healthy, mostly female young adults received intramuscular injections into the left arm of PRP-D (n = 27), HbOC (n = 19), C7p

Accepted for publication May 30, 1990.

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Table 1.—*Haemophilus influenzae* Type (Hib) Vaccines Used in a Comparative Immunogenicity Trial Among Infants, Children, and Adults.

Vaccine	Lot No.	Manufacturer	Type of Saccharide	Spacer	Amount of Hib Polysaccharide per Dose, µg	Protein-to-Polysaccharide Ratio
PRP-D	5L294 4102, 4163*	Connaught Laboratories Inc, Swiftwater, Pa	Sized polysaccharide†	6 carbon	20	1.25
HbOC	BrH-5-12, 6174‡	Praxis Biologics Inc, Rochester, NY	20-unit oligosaccharide	None	10	2.5
C7p	1 lot	Porter Anderson, Rochester, NY	7-unit oligosaccharide	None	5	5.0
PRP-T	S-1890	Institute Merieux, Lyons, France	Native polysaccharide	6 carbon	10	1.88

*Lot 4163 was used in infants and lots 5L294 and 4102 were used in adults and children.

†The molecular weight of the polysaccharide is heat sized to 200 to 2000 kd.

‡Lot 6174 was used in infants and lots BrH-5-12 and 6174 were used in adults and children.

(n = 18), or PRP-T (n = 21). No other vaccinations were given at the same time. Children were immunized intramuscularly into the right buttock at 23 to 25 months of age with PRP-D (n = 54), HbOC (n = 56), or C7p (n = 30). The children in the PRP-D group also received bivalent (groups A and C) meningococcal vaccine (Connaught Laboratories Inc, Swiftwater, Pa) and/or 23-valent pneumococcal vaccine (Pneumovax, Merck Sharp & Dohme, West Point, Pa); these vaccines have been shown to have no effect on the response to a Hib conjugate vaccine or to Hib CPS vaccine.^{22,24}

Serum Samples

Blood samples were obtained from infants before the first and second doses and 1 month after the second dose, ie, at 4, 6, and 7 months of age. Blood samples were obtained from children and adults before and 1 month after vaccination. The samples were preserved at -20°C until testing.

Follow-up of Adverse Reactions

The vaccinees were observed for at least 15 minutes after each vaccination. The vaccinees or their parents were given a special form to be completed 6, 12, 24, and 48 hours after vaccination. The rectal temperature, any systemic reaction, and description of local reactions at the injection site were recorded on this form.

Serologic Methods

Antibodies to the Hib PS were measured by a Farr-type radioimmunoassay²⁵ with the use of a tyramine derivative of Hib PS prepared by Rachel Schneerson (National Institutes of Health, Bethesda, Md) for iodination. The reference serum was also received from Rachel Schneerson.

Statistical Analysis

The geometric mean antibody concentrations (GMCs) were calculated with 0.06 mg/L as the lower and 320 mg/L as the higher limit of detection. Analysis of variance, Duncan's test at $P = .05$ (both tests need log-transformed data), and χ^2 test were used for differences in the anti-Hib PS antibody concentrations at each sampling point.

RESULTS

Reactogenicity of the Hib Vaccines

Irritability was the most common adverse effect among infants, reported in 41% to 60% of the vaccinees after the first dose and in 16% to 32% after the second dose. Fever was uncommon, detected in 2% to 5% of infants, regardless of age at the time of vaccination. Local soreness was also uncommon. No significant differences were noted between the vaccine groups regarding the frequency of reactions.

None of the adults or 2-year-old children had a fever after any of the vaccines. Local redness was reported in three children, and local soreness was reported in 14 chil-

dren, all of whom had received the PRP-D vaccine together with meningococcal vaccine and most of whom (n = 11) had also received the Pneumovax vaccine. These reactions were probably due to the latter vaccine.²²

Immunogenicity in Infants

Infants were immunized at 4 and 6 months of age. The preimmunization anti-Hib PS concentrations were similar (0.07 to 0.09 mg/L) in each group (Fig 1); few children actually had measurable antibody levels (Fig 2).

Two months after the first dose, at the age of 6 months, the anti-Hib PS concentrations differed significantly in the four vaccine groups ($P < .001$). The GMCs were only marginally higher than those measured before vaccination in the groups that had received either PRP-D, HbOC, or C7p vaccines (0.10, 0.09, and 0.10 mg/L, respectively). However, those who had received PRP-T showed an increase in anti-Hib PS concentration up to a GMC of 0.82 mg/L (Fig 1). At this time, only a few infants in the PRP-D, HbOC, and C7p vaccine groups but half of those in the PRP-T vaccine group had serum anti-Hib PS concentrations above 1 mg/L, and almost one fifth of the infants in the PRP-T group had concentrations higher than 4 mg/L (Fig 2).

At 7 months of age, 1 month after the second dose, the anti-Hib PS concentrations in the four groups differed significantly ($P < .001$). The GMCs in the HbOC, C7p, and PRP-T groups were similar (4.32, 3.10, and 6.10 mg/L, respectively), whereas the children who had received the PRP-D vaccine had a significantly lower GMC (0.63 mg/L; Fig 1). Most infants in the HbOC, C7p, and PRP-T groups had anti-Hib PS concentrations greater than 1 mg/L, and more than half of the infants had concentrations greater than 4 mg/L (Fig 2).

Immunogenicity in Adults and 2-Year-Old Children

All four vaccines listed in Table 2 elicited equally high anti-Hib PS antibody responses in adults. Among children immunized at 23 to 25 months of age, the postimmunization GMC was significantly higher after HbOC vaccine ($P < .01$) than after the other two vaccines. The recipients of the HbOC vaccine also had a significantly ($P < .05$) increased incidence of high antibody concentrations, exceeding 4.0 mg/L.

COMMENT

Significant differences were found between different Hib PS-protein conjugate vaccines given during infancy. Thus, the anti-Hib PS response was lower after two doses

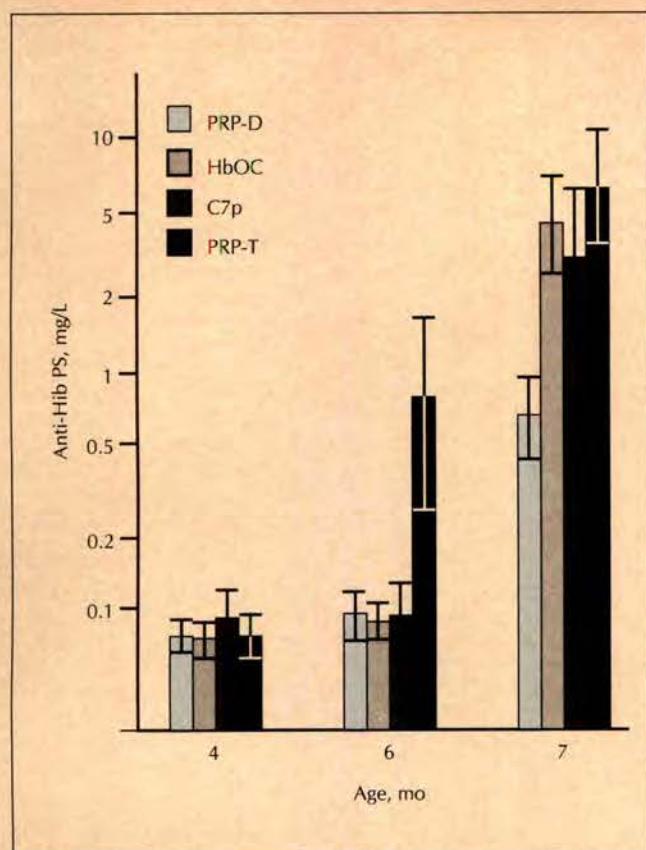


Fig 1.—Geometric mean antibody concentrations and their 95% confidence intervals (vertical lines) of serum anti-*Haemophilus influenzae* type b capsular polysaccharide (anti-Hib PS) in infants before (at age 4 months) and after (at ages 6 and 7 months) the first and second doses of one of the four conjugate vaccines against *H influenzae* type b (PRP-D, HbOC, C7p, or PRP-T). The vaccines were administered at 4 and 6 months of age.

of PRP-D than after two doses of the three other vaccines. Only the PRP-T vaccine gave rise to a significant antibody increase after the first dose given at age 4 months. In this respect, PRP-T may behave like PRP-OMP, which has also been reported to induce a response after one dose given at 2 to 6 months of age.¹⁸

The properties of a conjugate vaccine that determine its immunogenicity are unknown. The PRP-D and PRP-T vaccines proved to differ in immunogenicity despite the similarity of the PS and the coupling to protein; the protein partner was either diphtheria or tetanus toxoid.^{9,10} In the PRP-D vaccine, the protein was modified by incorporation of the adipic dihydrazide linker before the addition of the PS,⁹ whereas the linker in the PRP-T vaccine was first conjugated to the PS, which was then allowed to react with the protein.¹⁰ The increased immunogenicity of the PRP-T vaccine may thus be related to a more native protein structure; however, in both cases the protein was detoxified by formaldehyde before coupling. The quality of the protein carrier in the Hib PS- or OS-conjugate vaccine may also be important—in human infants, a conjugate prepared with CRM197 proved to be superior to one prepared with diphtheria toxoid,²⁶ and in infant rhesus monkeys conjugates with cholera toxoid were superior to those with tetanus toxoid or horseshoe crab hemocyanin.²⁷ Furthermore, the ratio of protein to PS in a PS-protein conjugate can influence its immunogenicity²⁸; the higher the ratio, the better the response, provided sufficient PS is present in one dose of vaccine. In our study, little difference was noted in the

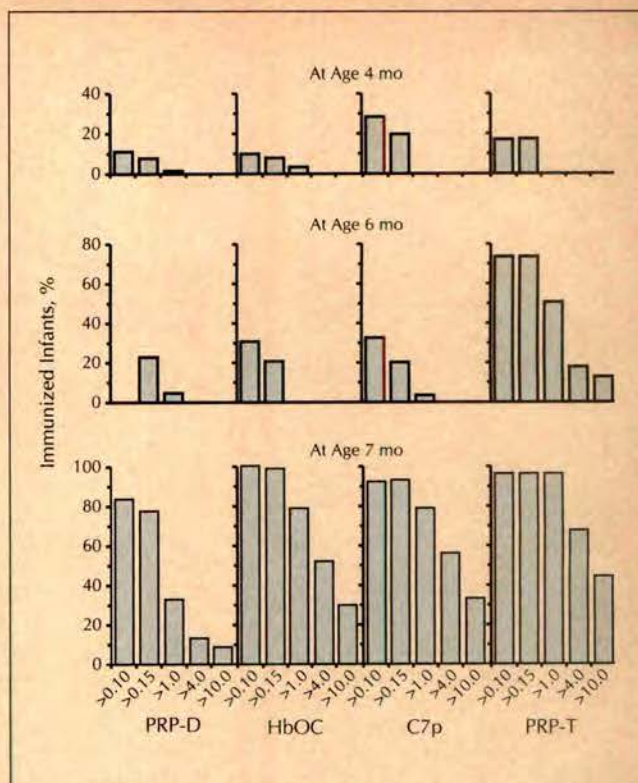


Fig 2.—Percentages of infants with anti-*Haemophilus influenzae* type b antibody concentrations above a set of indicated limits before and after the first and second doses of one of the four *H influenzae* type b conjugate vaccines (PRP-D, HbOC, C7p, or PRP-T). The samples and vaccinations are as shown in Fig 1.

Table 2.—Geometric Mean Anti-*Haemophilus influenzae* Type b Polysaccharide (Anti-Hib PS) Antibody Concentrations Before and After Immunization of Adults and 2-Year-Old Children With *H influenzae* Type b Conjugate Vaccines*

Vaccine	Anti-Hib PS, mg/L					
	Adults			Children		
	No.	Before	After	No.	Before	After
PRP-D	27	1.53 (0.97-2.42)	72.0 (45.3-114)	54	0.15 (0.11-0.20)	9.72 (6.72-14.1)
HbOC	19	2.58 (1.35-4.80)	85.5 (44.8-163)	56	0.19 (0.14-0.26)	30.6 (20.7-45.3)
C7p	18	1.90 (0.97-3.73)	63.3 (38.8-103)	30	0.14 (0.09-0.21)	11.2 (5.85-21.5)
PRP-T	21	0.86 (0.48-1.56)	29.8 (19.0-46.8)

*Values in parentheses indicate 95% confidence intervals.

ratio of protein to PS between the PRP-D and PRP-T vaccines (Table 1).

The HbOC and C7p vaccines both contain OS derived from Hib PS. Animal studies suggest that OS conjugates are more potent immunogens than PS conjugates.²⁹ These

and several other studies on human infants^{11,15,16,26} have shown that the Hib OS conjugate vaccines are good immunogens, even in infants. In the HbOC vaccine, the OS chains contain approximately 20 repeating units, and the C7p vaccine is seven repeating units long.¹² Within these limits, the length of the OS probably is not a critical factor, nor is the structure of the exposed termini.¹² The extent of OS loading is likely to be more important.¹² The similarity of the HbOC and C7p vaccines in our study also shows that the OS does not require a free terminus; in the HbOC vaccine, at least part of the OSs are bound to the protein biterminally,¹¹ while in the C7p vaccine, the binding is uniterminal.¹²

The disappointing message derived from this and other studies^{11,12} is that the antibody responses in adults and 2-year-old children cannot reliably predict immunogenicity of a Hib conjugate vaccine in infants. The same is true of plain PS antigens, all of which are good immunogens in those 2 years of age or older, but only conjugate vaccines serve as immunogens in infants. The reasons for this are not completely understood, but late maturation of those B cells responsible for the production of anti-PS antibodies has been suggested to be important.³⁰

It is also far from clear which characteristics of the immune response correlate best with clinical protection afforded by a conjugate vaccine. With the Hib PS vaccine, the situation was clearer: the protection was shown to correlate with the concentration of specific serum antibodies, and a concentration greater than 1 mg/L of anti-Hib PS was calculated to predict long-lasting protection after vaccination.^{31,32} In contrast, the PRP-D vaccine has been shown to be highly protective among Finnish infants,^{33,34} despite the relatively low antibody concentrations detected. In the field trial that showed protection in infants, the anti-Hib PS GMC at 7 months, after the course of three doses of PRP-D vaccine, was below 0.42 mg/L.³³ The best correlate of protection in that study was a measurable response of any magnitude (at least 0.1 mg/L of anti-Hib PS) obtained after the primary series of vaccinations in the infants. By this criterion, the PRP-D vaccine would be expected to be 80% to 90% protective vs 90% to 100% protection for the other vaccines (Fig 2) with the dosage and schedule used in our study.

This study was supported by Connaught Laboratories Inc, Swiftwater, Pa, Praxis Biologics Inc, Rochester, NY, and Institut Merieux, Lyons, France.

We thank the personnel in the Child Health Centers of Joensuu and Kerava for their valuable cooperation and the vaccinees and their parents for taking part in our study. We also thank P. Helena Mäkelä, MD, and Simon Kroll, MD, for fruitful discussions and their critical reading of the manuscript. The skillful assistance of Hannele Lehtonen and Sirkka-Liisa Wahlman and the help of Mari-Anna Berg, MSc, and Panu Rekola, MSc, in the handling of the data is gratefully acknowledged.

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Focal Scleroderma and Severe Cardiomyopathy

Patient Report and Brief Review

Ellen C. Moore, MD; Flossie Cohen, MD; Zia Farooki, MD; Chung-Ho Chang, MD

• A 21-month-old infant presented with simultaneous localized scleroderma and severe cardiomyopathy with heart failure. Cardiac abnormalities and serological changes (positive rheumatoid factor assay, elevated IgM and IgG levels, and elevated erythrocyte sedimentation rate) reverted to normal with prednisone therapy, and there was substantial, though incomplete, resolution of her skin changes during the same period. To our knowledge, this is the first patient with definite, clinically significant cardiac involvement associated with focal scleroderma. The possibility of internal organ involvement, including cardiac involvement, must be considered with focal scleroderma as well as with progressive systemic sclerosis.

(AJDC. 1991;145:229-231)

Focal scleroderma is a rare disorder, more commonly encountered in children than in adults.¹ It is usually benign, without apparent systemic involvement, but does form a continuum with generalized scleroderma (progressive systemic sclerosis [PSS]), where involvement of organs other than skin is common. Involvement of brain,² gastrointestinal tract² (especially the esophagus^{3,4}), lung,^{3,4} muscle,^{4,5} and kidney⁴ has been reported rarely in focal scleroderma. Serological abnormalities⁶⁻¹¹ also suggest this disorder is not limited to skin and underlying tissues.

In PSS, involvement of the heart may occur in up to 81% of the cases,¹² although it is clinically apparent only in about 15% and may be more common in children than in adults.¹³ Two of three patients with morphea studied by echocardiography¹⁴ also showed cardiac abnormalities, and sclerodermatous myocardial involvement on autopsy was found in an elderly patient with morphea described by Rodnan and Fennel⁵ (case 4), though it is unclear whether her cardiac symptoms were due to the scleroderma per se, as she also had had multiple myocardial infarctions. To our knowledge, the infant described herein

is the first patient with definite, clinically significant cardiac involvement associated with focal scleroderma.

PATIENT REPORT

In a previously well Mexican-American girl, at 19 months of age, white blotches developed over her axillae, legs, and buttocks, and she gradually became unable to extend her legs fully. Her weight decreased from 14.0 to 11.7 kg. At 21 months, when she came for medical attention, she had white, hard, plaque-like skin in both axillae and similar, more confluent lesions on her legs and ankles (Fig 1). This skin was tense and adherent to the underlying structures, with loss of subcutaneous tissue and muscle atrophy. The remainder of her skin was normal. Marked flexion contractures were noted bilaterally on her knees and hips. Her right foot was fixed in equinus position with a limited range of motion. The left foot was somewhat more mobile than the right foot, but also had an equinus deformity, with a high arch because of the tight, adherent skin.

She was mildly febrile (temperature, 37.8°C), tachycardic (heart rate, 160 beats per minute), and tachypneic (respirations, 28 to 35 per minute). No significant murmur was heard, but a soft S₃ gallop was present. Her liver was palpable 3 cm below the costal margin, and pedal edema was present. Her hemoglobin level was 102 g/L. White blood count cell was $14.0 \times 10^9/L$, with granulocytes, 0.33; lymphocytes, 0.60; eosinophils, 0.04; and basophils, 0.03. Erythrocyte sedimentation rate (ESR) (Wintrobe) was elevated, IgG and IgM levels high, and rheumatoid factor assay (Organon) positive (Table). Antinuclear antibody assay was negative on peripheral blood and HEP-2 cells.

Chest roentgenography showed a generally enlarged heart (cardiothoracic ratio, 0.6) with vascular congestion. Echocardiographic examination revealed a moderately enlarged and non-hypertrophied left ventricle with depressed contractility (Table). Her left atrium was also enlarged. No pericardial effusion was noted. The electrocardiogram showed slightly decreased voltages, nonspecific T-wave changes, and sinus tachycardia. Anti-streptolysin O titer, anti-DNAse, and antibodies to Epstein-Barr virus, toxoplasma, and varicella zoster were not detected. Only low titers of antibody were found to rubella, adenovirus, and cytomegalovirus. Acute and convalescent titers to coxsackievirus B1 through 6 showed no significant interval change.

Biopsy of the affected area of her legs (Fig 2) showed varying degrees of perivascular lymphocytic infiltration around the dermal capillaries and interstitial fibrosis. Increased cellularity was also noted around dermal appendages. The fascia and subcutaneous fat were severely inflamed, with some inflammation of the muscle itself, and diffuse interstitial fibrosis accompanied by hypertrophy of muscular arteries in the fibrofatty tissue around the muscle. Several small vessels in the perimysium showed mild perivascular lymphocytic infiltration. Immunofluorescent staining for immunoglobulin deposition and C3 was negative, and electron microscopy showed no immune complexes or viruslike structures.

During the next month, with 2 mg/kg per day of prednisone

Accepted for publication July 16, 1990.

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Fig 1.—The patient at 21 months. The involved areas are hypopigmented and indurated. Contractures are present in knees, hips, and ankles.

given as 9 mg orally three times daily, digoxin (Lanoxin), and physical therapy to her legs, the patient became less irritable and had some increase in range of motion. Her cardiac gallop disappeared, and her left atrium and ventricle decreased in size, though severely depressed left ventricular function remained. A right-sided Horner's syndrome developed. The initially positive rheumatoid factor assay became negative, and the ESR became normal during the first month.

After 6 weeks, the dose of prednisone was slowly tapered. The IgM level, which initially increased to 7.70 g/L after 6 weeks of therapy, decreased over several months. The elevated IgG level became normal after about 2.5 months. The ESR rose again in the third month, when the mother inadvertently and abruptly decreased the steroid dose. The ESR promptly returned to normal as prednisone therapy was resumed. By 4 months after the initiation of treatment, the child had a completely normal heart by clinical examination, chest roentgenography, and echocardiogram (Table) and had regained sufficient mobility of her legs to resume walking.

The digoxin therapy was discontinued at 15 months and the prednisone therapy at 16 months. The abnormal skin in the axillary areas became normal to the touch and hyperpigmented rather than white.

Although the skin on her legs remained tight, it became less hard and hyperpigmented rather than white (Fig 3). Her right ankle remained essentially fused in equinus and required later surgical release to improve her gait. The Horner's syndrome became inapparent, though the mother has reported occasional drooping of the child's eyelid. Seven years after presentation, the child has had no further internal organ involvement, and her skin disease has shown no further progression.

Cardiac and Laboratory Findings Initially and After 4 mo of Therapy

	Initial Findings	At 4 mo
L ventricular end-diastolic volume index, mL/m ²	162	75
shortening fraction	0.17	0.36
ejection fraction	0.35	0.67
Aortic preejection time/ejection time	0.56	0.32
Cardiothoracic ratio	0.6	0.51
Erythrocyte sedimentation rate (Wintrobe)	44	8
IgG, g/L	31.00	8.60
IgM, g/L	4.26	2.80 (at 7 mo)
Rheumatoid factor	1:80	Negative
Antinuclear antibody	Negative	Negative



Fig 2.—Microphotograph of perifascial tissue. Note the diffuse fibrosis of perifascial subcutaneous tissue with chronic inflammatory infiltrates (arrow; F indicates fascia; hematoxylin-eosin, $\times 40$).

COMMENT

A coincidental viral myocarditis in this patient cannot be totally excluded; also, that a viral agent may have initiated both processes must be considered, though we did not succeed in identifying a candidate virus for this role. However, the reports of echocardiographic changes with focal scleroderma,¹⁴ the sclerodermatous changes in the heart in the patient of Rodnan and Fennel,³ and the rarity of both cardiomyopathy and focal scleroderma suggest that the association of the two in our patient may be more than coincidental.

It may be debated that internal organ involvement together with any type of skin finding of scleroderma should be considered PSS, but the morphea plaques in the axillae and the involvement of the skin, subcutaneous tissue, and muscle of the legs and feet in our patient were characteristic of linear scleroderma^{5,15} and unlike the skin changes in PSS. Also, there has been no subsequent involvement of internal organs in 7 years of observation, and her skin involvement has not progressed further.

Focal scleroderma, if sufficiently localized, often requires no specific treatment and may undergo spontaneous remission or arrest, with approximately 80% of patients no longer having persistent or recurrent activity after the first 2 years.¹ Children with limb contractures



Fig 3.—At 36 months, the skin had become hyperpigmented rather than white. Contractures are limited to the ankles. There has been further loss of subcutaneous tissue, particularly on the right lower leg and the medial side of the left foot.

may benefit from an intensive physical therapy program to decrease residual deformity, and some patients later require surgery to improve function.

In some instances, where the disease is progressive and appears likely to be cosmetically or functionally disastrous, or both, or is associated with some form of systemic involvement, definitive treatment would be desirable. As in PSS, no really definitive treatment is known.

Corticosteroids are generally found ineffective, though in some cases^{2,15-19} improvement is reported. Improvement is thought more likely where inflammation (rather than fibrosis) is more pronounced and more acute.¹⁶ This child had a short history and had laboratory evidence of inflammation. Though it cannot be proved that the prednisone was responsible for her improvement, her prompt response in the face of severe illness makes it likely. The brief flare-up in her ESR in the third month when her mother inadvertently and markedly decreased the dose also suggests the effect of prednisone. Although it cannot yet be predicted which patients with focal scleroderma might respond, a trial of steroids may be warranted in the more severely afflicted patients, especially when the disease appears to be acute and inflammatory.

Other agents that have been proposed for the treatment of focal scleroderma include sulfasalazine,²⁰ etretinate,²¹ and penicillamine.²² The last drug, which appears the most promising, has received several recent favorable reports regarding its use in PSS.¹ It interferes with the intramolecular cross-linking of collagen and is also immunosuppressive. It may be worth trying when progressive fibrosis is likely to cause severe morbidity. This drug has

multiple potential side effects, however, and must be carefully monitored.

In summary, we report the case of an infant with focal scleroderma and cardiomyopathy. The possibility of internal organ involvement, including cardiac involvement, must be considered with focal scleroderma as well as with PSS.

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Chronic Neutropenia During Childhood

A 13-Year Experience in a Single Institution

Olafur G. Jonsson, MD, George R. Buchanan, MD

● To evaluate the clinical course and characteristics of children with chronic neutropenia, we reviewed the charts of all such patients seen at our center during a 13-year period. A total of 50 patients with chronic neutropenia were identified. Three patients had documented congenital neutropenia, and two siblings had cyclic neutropenia. The remaining 45 children had chronic neutropenia of unknown origin. All children except two had a remarkably benign course despite markedly reduced granulocyte counts. Of six girls in this group who had abscess or cellulitis of the labia majora, it was a presenting manifestation in three. Resolution of neutropenia was documented in 23 (62%) of 37 patients for whom follow-up information was available, with a median duration of neutropenia of 19 months. No differences were evident between patients with positive antineutrophil antibody test results and those in whom the test yielded negative results or was not performed. Chronic neutropenia in childhood is a relatively uncommon entity, characterized by a benign course and eventual resolution in the majority of patients.

(AJDC. 1991;145:232-235)

The chronic neutropenias of childhood are a group of disorders with a variable clinical course, ranging from death in early infancy to a benign condition often discovered incidentally.¹⁻³ The etiology, pathogenesis, natural history, and relative incidence of childhood neutropenia have been unclear, as reflected by confusing nomenclature^{4,5} and a lack of general reviews of chronic neutropenia describing overall experiences at a single institution. We have noted that some children initially diagnosed as having congenital neutropenia subsequently had spontaneous and permanent remissions, seemingly inconsistent with the diagnosis.⁶ In an attempt to clarify some of these uncertainties regarding chronic neutropenia and to identify common features among these patients, we reviewed the charts of patients with neutropenia seen at our center during a 13-year period. We found that most children with chronic idiopathic neutropenia had a relatively benign course that was indistinguishable from that described previously for patients with autoimmune neutropenia.

Accepted for publication March 19, 1990.

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PATIENTS AND METHODS

All patients referred for consultation to the Division of Hematology-Oncology at the Children's Medical Center of Dallas, Tex, from January 1, 1977, to December 31, 1989, with the primary diagnosis of neutropenia were identified from departmental files. Patients with other primary diagnoses known to cause neutropenia (eg, leukemia, preleukemic states, aplastic anemia, collagen-vascular disease, and hypersplenism) were not included in this listing even though neutropenia might have been noted at some time during their illnesses. Inpatient and outpatient charts on all patients were reviewed, with particular attention directed to the duration and severity of neutropenia, possible underlying diseases, frequency and severity of infection, and exposure to drugs. Physical findings were recorded, as were results of serial complete blood cell counts, serum immunoglobulin measurements, and antineutrophil antibody tests. Results of bone marrow examinations were obtained from pathology reports. Serum antineutrophil antibody levels were measured at the University of Michigan, Ann Arbor, using an indirect immunofluorescence assay.⁷ Every effort was made to obtain follow-up information on patients by contacting their primary physicians.

Neutropenia was defined as an absolute neutrophil count (absolute neutrophil count equals the percent of neutrophils and band cells times the total white blood cell count divided by 100) of less than $1.5 \times 10^9/L$.⁸ Chronic neutropenia was defined as neutropenia lasting more than 8 weeks. Patients were classified as having congenital neutropenia only when a complete blood cell count documenting neutropenia was available before age 3 months and the neutropenia persisted.

RESULTS

During this 13-year period, 101 patients were listed as having a primary diagnosis of neutropenia, as shown in Table 1. Fifty of these patients had chronic neutropenia and 51 had transient neutropenia. We will not discuss the patients with transient neutropenia.

Two siblings had cyclic neutropenia. One of them died at age 5 years of *Staphylococcus aureus* septicemia; the other was alive at age 6 years with relatively few infectious complications. Only several familial cases of cyclic neutropenia have been described previously.^{9,10}

Three patients had congenital neutropenia. One of them had *S aureus* septicemia as an infant but has done well except for frequent episodes of otitis media, skin infections, and gingivitis. He remained profoundly neutropenic at age 16 years, but recently was treated with recombinant granulocyte colony-stimulating factor, with normalization of his neutrophil count.¹¹ The other two patients with congenital neutropenia are identical twins who were both noted to be neutropenic at birth. They were

Table 1.—All Patients With a Primary Diagnosis of Neutropenia Seen at Children's Medical Center of Dallas, 1977 Through 1989

Type of Neutropenia	No. of Patients
Chronic	
Congenital	3
Cyclic	2
Severe	2
Other (benign)	43
Total	50
Transient	
Viral infection	16
Drugs	12
Underlying disease	8
Neonatal	7
Other	8
Total	51

aged 9 years at the time of this report and remained neutropenic (absolute neutrophil count, approximately $0.5 \times 10^9/L$) but have had few infectious complications.

Clinical Features

The remaining 45 patients are the main subjects of this report. They were generally healthy infants who came to medical attention because of fever and recurrent minor infections and were then found to be neutropenic. Only two patients had severe and recurrent infectious complications; both had measurable antineutrophil antibodies in their serum. One patient was a 6-year-old white girl with massive lymphadenopathy and hepatosplenomegaly and recurrent mouth ulcers; her bone marrow aspirate showed maturation arrest at the promyelocyte stage. She continued to be severely neutropenic despite various therapeutic interventions, including corticosteroids, intravenous immunoglobulin, and granulocyte-macrophage colony-stimulating factor, but at age 9 years the neutropenia had resolved concomitantly with cyclosporin A treatment. The other severely affected patient was an 8-year-old boy with profound neutropenia whose bone marrow aspirate showed granulocyte aplasia¹² but otherwise normal elements. He responded temporarily to prednisone therapy but remained markedly neutropenic and died of pneumonia and sepsis 6 weeks after the administration of antithymocyte globulin at another institution.

The median age of these 45 patients at the onset of neutropenia was 12 months (range, 3 to 144 months). Thirty-six (80%) of the 45 patients were younger than age 24 months when neutropenia was diagnosed. The male:female ratio was 1:1. Infections were frequent in this group of patients but they were generally mild (eg, upper respiratory infections, otitis media, and skin infections). One patient had periorbital cellulitis and another had one episode of pneumonia.

As listed in Table 2, six of the 23 girls in this patient population had an abscess or cellulitis involving the labia majora at some time during the duration of neutropenia. This infection was a presenting manifestation in three of these patients. *Pseudomonas aeruginosa* was cultured from three of these children. One patient had recurrent *Pseudomonas* labial infections. Invasive bacterial infections other than those mentioned above were not observed.

The physical examination was unremarkable in most patients with chronic neutropenia, with the exception of mild splenomegaly in six patients. One of the two severely affected patients had massive hepatosplenomegaly, and

Table 2.—Cellulitis or Abscess Involving the Labia Majora in Girls With Chronic Idiopathic Neutropenia

Patient	Age, mo*	Duration of Neutropenia*	Organism	Antineutrophil Antibody Test Results
1	15	At onset	Unknown	Negative
2	66	12 mo	<i>Pseudomonas aeruginosa</i> (with positive blood culture)	Positive
3	11	3 mo	Unknown	Not performed
4	9	At onset	<i>P aeruginosa</i>	Not performed
5	6	At onset	<i>P aeruginosa</i> (three episodes)	Positive
6	7	2 mo	Unknown	Positive

*When labial lesion occurred.

prominent lymphadenopathy was noted in four children. Recurrent gingivitis or mouth ulcers were a significant complaint in only three patients.

Laboratory Studies

Neutrophil counts were extremely low in all patients. The lowest recorded absolute neutrophil count was unmeasurable in nine patients; less than $0.2 \times 10^9/L$ in 34 (76%) of 45 children; and less than $0.5 \times 10^9/L$ in all but two patients. The median lowest value for the group was $0.1 \times 10^9/L$. Very low absolute neutrophil counts persisted in most patients, with temporary fluctuations into the normal range observed only occasionally.

An increased percentage of circulating blood monocytes was noted intermittently, but the number of monocytes did not clearly correlate with the degree of neutropenia or the presence of infection.

The median hemoglobin level at presentation was 118 g/L (range, 90 to 138 g/L). The hemoglobin concentration was more than 100 g/L in all but four patients, one of whom had β -thalassemia trait and two of whom had documented iron deficiency. Platelet counts were normal or mildly elevated in all patients.

Quantitative serum immunoglobulin levels were measured in 23 of the 45 patients and were within normal limits in 12 patients and only slightly elevated in another nine patients. One of the severely affected patients had a low IgA level and a high IgM level, and another patient had low IgG levels.

Serum antineutrophil antibody measurements, performed in 28 of the 45 patients, were positive in 13 patients and negative in 15 patients. There was no relationship between the severity of symptoms of neutropenia and the presence or absence of antineutrophil antibodies. As indicated in Table 3, no other differences could be detected between groups when patients were classified according to the antineutrophil antibody test result.

Bone marrow aspiration was carried out in 31 patients. In 28 of these patients the bone marrow was entirely normal or had only decreased numbers of neutrophils. Both of the severely affected patients described above had maturation arrest at an early stage in granulocyte development. Only one mildly affected patient had an early granulocyte maturation arrest.

Table 3.—Characteristics of Patients With Chronic Idiopathic Neutropenia

Characteristic	All Patients (N = 45)	Antineutrophil Antibody Results		
		Positive (n = 13)	Negative (n = 15)	Not Performed (n = 17)
Male-female ratio	22:23	5:8	9:6	8:9
Mean age (range) at diagnosis of neutropenia, mo	12 (3-144)	10 (3-92)	16 (6-144)	12 (6-132)
Mean age (range) at resolution, mo	38 (10-114)	38 (10-114)	38 (21-86)	34 (15-72)
Mean duration (range) of neutropenia, mo	19 (6-64)	19 (7-45)	27 (11-61)	14 (6-64)
Mean (range) lowest recorded absolute neutrophil count, $\times 10^9/L$	0.1 (0-0.52)	0.1 (0-0.27)	0.1 (0-0.34)	0.12 (0-0.52)
No. of patients with splenomegaly	7	2	2	3
No. of patients with normal or near normal* bone marrow	28	8	11	9
No. of patients for whom resolution of neutropenia was documented	23	9	6	8
No. of patients in whom neutropenia did not resolve	13	0	7	6

*Reduced number of neutrophils the only abnormality.

Treatment and Outcome

All of these children were treated with supportive measures and antibiotics (usually oral) for febrile illnesses. Only two patients received prophylactic antibiotic treatment at the decision of the referring physician. It is noteworthy that bacterial pneumonia was diagnosed in just one of 43 patients; the two severely affected patients had several episodes of lower respiratory tract infections. The only other cases of invasive bacterial infections included one episode of periorbital cellulitis and infections of the labia majora in six girls. The frequency of minor infections lessened with age in almost all patients.

Excluding the two severely affected patients, only 12 of the 43 children with chronic neutropenia were hospitalized, for a total of 18 admissions. Eleven of these hospitalizations were for initial diagnostic evaluation.

Four patients were treated with corticosteroids. The two severely affected patients described above responded poorly. One of the two other patients did not respond, but the other had partial resolution of neutropenia and healing of mouth ulcers, which recurred when prednisone therapy was discontinued. Intravenous immunoglobulin preparations were given to the two severely affected patients without response.

Follow-up information was available on 37 children, as outlined in Table 3. In 23 (62%) of these children, resolution of the neutropenia was documented, with a median duration of neutropenia of 19 months. The median age at resolution was 38 months. Thirteen children were still neutropenic at last contact, with a median period from diagnosis to last available blood cell count of 18 months. Three of these 13 patients had normal blood cell counts documented before the onset of neutropenia. One patient died, and follow-up information was not available on the eight remaining patients. Excluding the two severely affected patients, the remaining 35 children on whom follow-up information was available were in good health.

COMMENT

Although neutropenia during childhood has many definable causes, there exists a large group of patients in whom no clear cause can be identified. It has been recognized that many of these patients with chronic idiopathic neutropenia have a benign clinical course, and only a minority of patients have severe recurrent infections.^{4,13-16} Bacterial infections, although increased in

frequency, are generally mild and usually respond well to antibiotic treatment; mortality is low or absent.^{4,13-16} Such a benign course was evident in most of our patients with chronic neutropenia.

Autoimmune neutropenia has been recognized increasingly during the past several years.¹⁶ An ill-defined entity called "chronic benign neutropenia" is very similar in presentation and clinical course to autoimmune neutropenia.^{15,16} It has been suggested that most of these cases are actually autoimmune in origin and pathogenesis even though antineutrophil antibodies may not always be demonstrated.¹⁵ Technical difficulties in performing antineutrophil antibody tests are well recognized, and the sensitivity and specificity of these assays have not been well defined.⁷ No apparent difference existed in this study between patients with chronic neutropenia who did and did not have antineutrophil antibodies detectable in their serum. Thus, it seems possible that most children with chronic neutropenia of unclear origin have a disorder caused by immune mechanisms despite negative antineutrophil test results.

To our knowledge, cellulitis involving the perirectal area, groin, or face caused by *Pseudomonas* has been reported just once in association with chronic neutropenia.⁶ Two additional reports mentioned an infection of the vulva or Bartholin's gland, but the offending organism was not stated.^{2,15} It is noteworthy that six (26%) of the 23 girls in our series had abscess or cellulitis involving the labia majora at one time or another during the course of their disease. In three patients, *P. aeruginosa* was documented as the offending organism. This is a very unusual infection in healthy girls and clearly should lead to the suspicion of neutropenia when encountered clinically.

Maturation arrest at an early stage of granulopoiesis has been described in the bone marrow of some patients with chronic neutropenia.^{7,12} Bone marrow examination in our patients usually showed normal myeloid maturation except for decreased numbers of segmented neutrophils, a feature previously noted to be associated with autoimmune neutropenias.^{4,15,16} Our data suggest that infants with the typical features of chronic idiopathic (presumably autoimmune) neutropenia may not require a routine bone marrow aspiration for purposes of diagnosis and treatment. However, the presence of any other abnormalities on the complete blood cell count should definitely prompt

a bone marrow examination to exclude acute leukemia, aplastic anemia, or a myelodysplastic state.

All of our patients responded well to standard supportive measures. Intravenous γ -globulin and corticosteroids have been reported to induce temporary remissions in some children with autoimmune neutropenia,^{16,17} but treatment with these agents should probably be reserved for those rare patients who manifest severe or especially frequent infectious complications. Recombinant hematopoietic growth factors, such as granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor, may, in the near future, play an important role in the treatment of severely affected patients with congenital and other forms of neutropenia,¹¹ but will not be required for most children with chronic neutropenia.

This review does not allow an accurate estimate of the incidence of chronic neutropenia in childhood, but it does suggest that it is a relatively uncommon condition, since only 45 patients were diagnosed during a 13-year period in the only pediatric hematology referral center serving a population of 3.5 million people. Congenital neutropenia is an uncommon entity and may be overdiagnosed. Young children incidentally found to be neutropenic are more likely to have an autoimmune disorder than a congenital neutropenic state. Only one of our patients with congenital neutropenia had features consistent with Kostmann's syndrome or infantile genetic agranulocytosis.³

Most children with chronic neutropenia, irrespective of antineutrophil antibody test results, have a remarkably benign disorder that often eventually resolves. We propose that most such patients have an autoimmune disorder rather than a congenital neutropenic state.

This work was supported in part by the Children's Cancer Fund of Dallas, Tex.

We thank Dawn Miller and Patricia Ellisor for their expert secretarial assistance, and physicians in North Texas for referring their patients and providing follow-up information.

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CALIFORNIA — NEONATOLOGIST BC/BE. Two positions available with active neonatal group, 12,000 delivery base with tertiary and secondary level positions. Excellent practice opportunity for neonatologist desiring relocation in southern California. Contact: Doctors of Newborn Critical Care, 721 North Euclid Avenue, Suite 308, Anaheim, CA 92801. (714) 772-4822.

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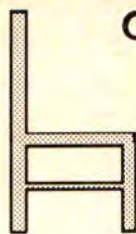
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Nominations and applications should be addressed to David Lagunoff, M.D., Chairman of the Search Committee, 301 Caroline, St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, MO 63104. (314) 577-8108



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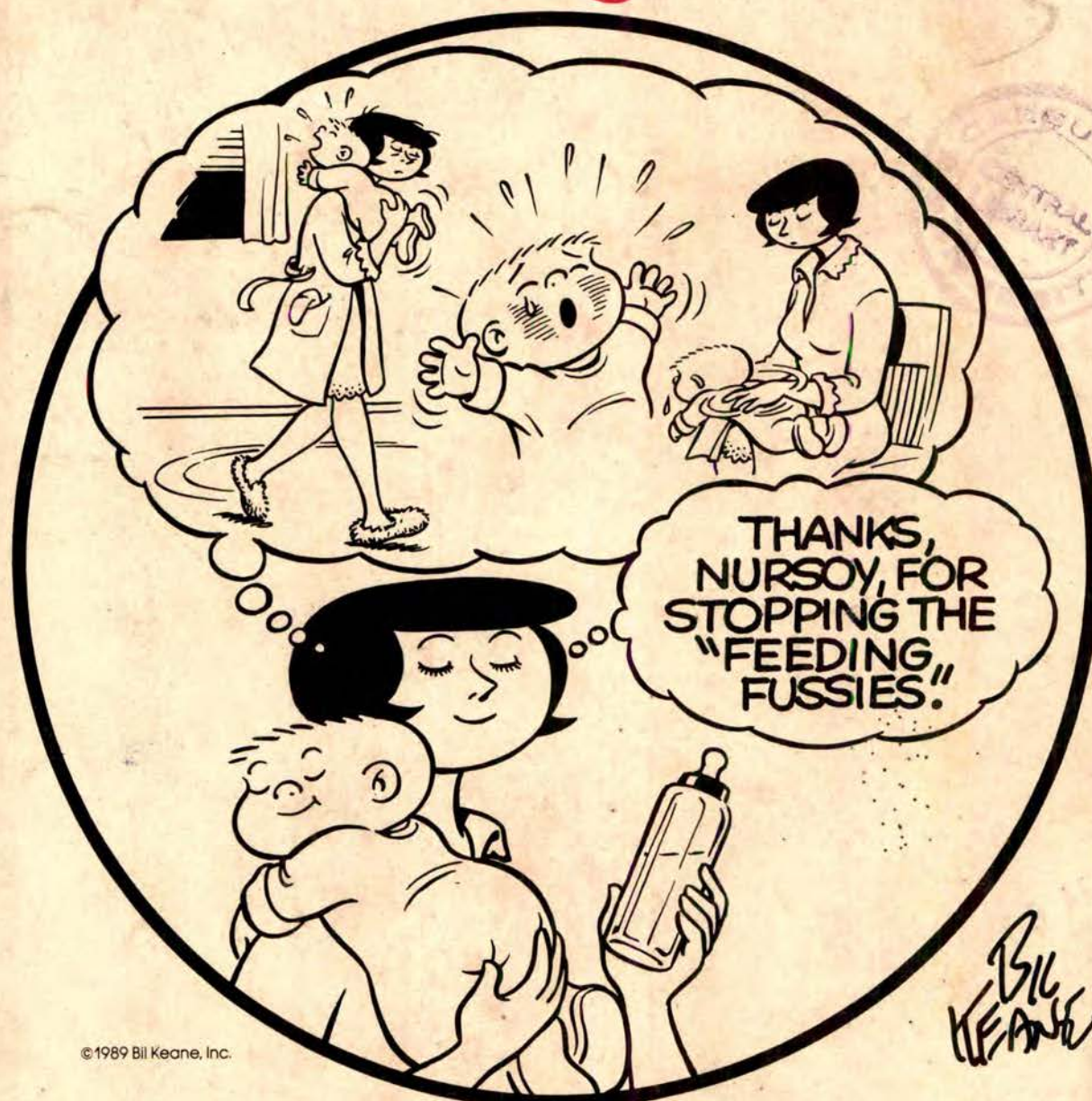
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V. K. Wong, R. Quagliata, R. Adler, K. S. Kim

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**Apparent Decreased Risk of Invasive Bacterial Disease
After Heterologous Childhood Immunization**

S. B. Black, J. D. Cherry, H. R. Shinefield, B. Fireman,
P. Christenson, D. Lampert

**A Comparative Trial of the Reactogenicity and
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Combined With Tetanus and Diphtheria Toxoids:
Outcome in 3- to 8-Month-Old Infants, 9- to 23-Month-Old
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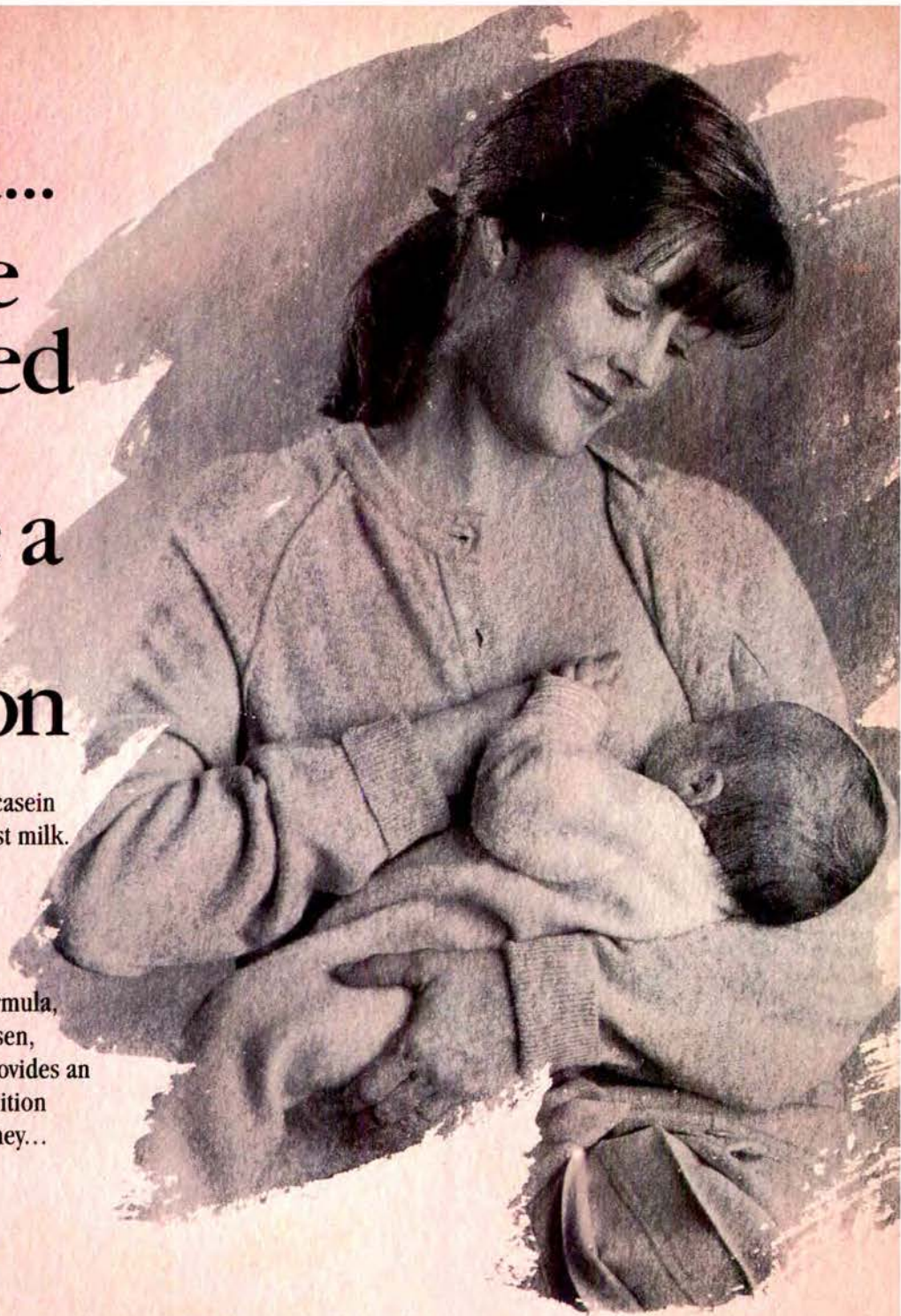
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G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Overdosage: Signs and Symptoms: Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2 1/2-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2 1/2-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

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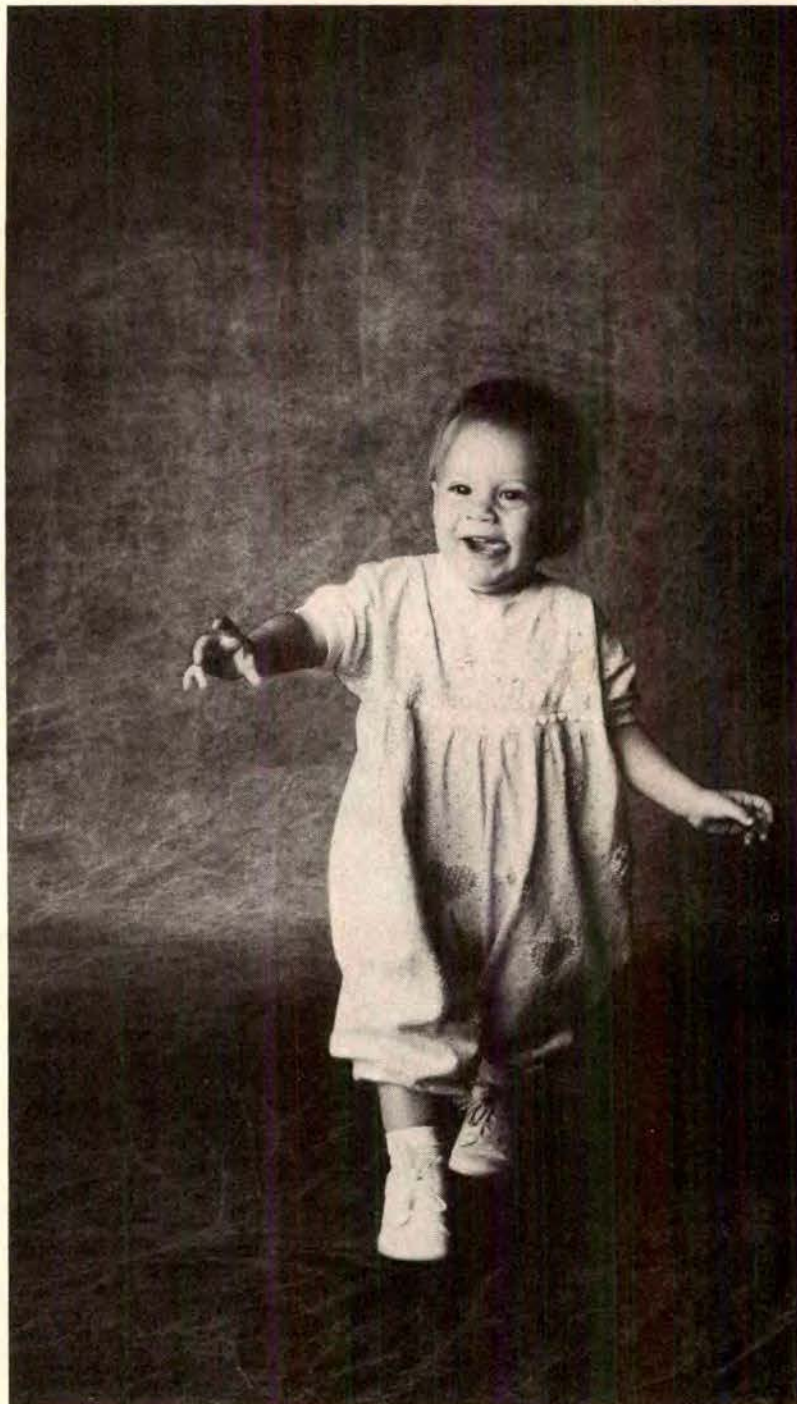
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More on a Myth

Sir.—I read your very interesting editorial in the August 1990 issue of *AJDC*¹ on the pertussis vaccine myth and its death.

I have been practicing pediatrics for 30 years in West Texas and have administered the diphtheria and tetanus toxoid and pertussis vaccine to more children, I am sure, than many physicians in the academic centers. I have probably examined more children than many of the physicians in institutional centers. I have never seen a reaction supporting the findings of encephalopathy that were previously thought to occur in conjunction with diphtheria/pertussis immunizations, particularly pertussis immunizations.

What disturbs me most about your editorial is your discomfort with the fact that there are many unexplained results in medicine leading the "experts" to render opinions that become irrefutable early on, to the degree that they are used by courts of law to hold the practicing physician responsible for injury and therefore financially liable. This is one of the facets that, in my opinion, have led to the high cost of liability. "Cap-and-gowned" experts around the country continue to give their opinions even before evidence is collected on whether a complication is associated with the performance of certain procedures, the application of certain treatments, or the provision of certain medications to patients, thereby creating a situation that is very hard to turn around when an untoward event occurs. It would be certainly more efficacious, safer, and better if the "experts" refrained from making official statements and giving their opinions before having clear evidence to support such definite pronouncements early in the course of any illness.

As a result of the concern for pertussis vaccine and so-called myth of encephalopathy, the fear of God was

placed on pediatricians' shoulders. The fear of litigation along with the concomitant rise in the cost of liability and vaccines has put the pediatric community in a position from which it may never recover. In terms of reasonable medical liability insurance coverage fees and affordable immunizations to patients as administered by the private and public pediatric community, I doubt very seriously if, in a free market economy, the price of those vaccines or liability costs will decrease in the face of such a myth. It is so interesting to me that in these United States, myths have such a great degree of control over us that they often explain untoward outcomes more than reality.

Please note also that as a result of the myth, a Vaccine Compensation Act was passed at extreme cost to the providers of care, drug manufacturers, and other entities. It was probably unnecessary in the first place. It appears now that the people who will benefit from the passage of such a law and the creation of such a fund are the managers of the fund and attorneys who, through the process, know how to tap into that fund. I am sure if we now decided that the compensation fund was unnecessary, the money would never be refunded, and even if it were, any savings would not be returned to the people who originally participated in contributing to that fund.

I doubt that my letter will be read with the intent that is meant; I doubt that it will be published; and I also doubt very seriously whether anyone in the academic field and the so-called experts of medicine will get the message.

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1. Fulginiti VA. A pertussis vaccine myth dies. *AJDC*. 1990;144:860-861.

In Reply.—I appreciate Dr Roman's letter in response to my editorial concerning the pertussis vaccine enceph-

alopathy myth. His comments are those of a concerned physician and should be taken seriously. To add further information to the topic he discusses, I refer Dr Roman to my earlier editorial on how standard practice in pediatrics is set.¹

I do not believe that experts act capriciously. I addressed part of this in my previous editorial, but would like to take this opportunity to expand on those thoughts.

Most experts are dedicated professionals who strive to offer their best opinion in a discipline that does not have all the data it needs but must act on the data available to care for patients. My experience is mostly with recommendations for immunization and infectious diseases practice, so I will draw on that for my examples.

The Academy of Pediatrics Committee on Infectious Diseases (the "Red Book" Committee) serves pediatricians by digesting, analyzing, and sorting out the available data on infectious diseases and their prevention and treatment. From this process they develop recommendations for the practitioner by consensus. These are incorporated into the *Red Book* and other statements published by the committee from time to time. The preamble to the latest edition of the *Red Book* states

Unanswered scientific questions, the complexity of medical practice, new information, and inevitable differences of opinion between experts result in inherent limitations in the *Red Book*. Other committees and experts may not always agree with specific recommendations of the committee and will provide different viewpoints. . . . Inevitably in clinical practice, questions arise which cannot be answered on the basis of currently available data, but in such cases the committee attempts to provide guidelines and information that in conjunction with clinical judgment will facilitate well-reasoned decisions.²

This statement, built on earlier versions published in previous editions of the *Red Book*, summarizes my own viewpoint on the issue that Dr Roman

raises. The individual practitioner often requests some guidance in areas in which he or she does not have all the available information. Experts and advisory committees attempt to assist by providing the best possible advice. This is precisely what happened with the pertussis vaccine encephalopathy story. As I outlined in my editorial, in the days before we had the data now available, the best analysis was that such an entity existed. It was not irresponsible opinion, it was the best judgment that could be rendered. It was not delivered capriciously or with the intent of harming the practitioner. On the contrary, the opinion was offered to assist the practitioner in avoiding this possible complication by delimiting those children who might be vulnerable (in the form of recommendations for precautions and contraindications for the use of whole-cell pertussis vaccine).

Unfortunately, much of medical expert advice today in all areas of medicine has the same indefinite characteristic. Data are incomplete, significant critical gaps exist, and yet, patients must be treated, vaccines administered, and other forms of treatment provided. Experts, rather than remain silent and indecisive, should offer their opinions. I agree with Dr Roman that the potential consequences of those opinions should be carefully weighed and taken into account, and appropriate qualifications offered. That is precisely what the *Red Book* statement quoted above attempts to do. That society, through the tort system, chooses to act on those opinions cannot be helped. The American Academy of Pediatrics, along with other interested parties, attempted to influence this societal tendency by advocating, assisting in developing, and participating in implementing the Vaccine Injury Compensation Act and Program.

In short, I believe experts need to give their best opinion in areas that are uncertain, and that such opinions indicate the degree of uncertainty and take into consideration potential consequences.

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1. Fulginiti VA. Is standard practice in pediatrics 'standard': a potential lesson for experts and practitioner. *AJDC*. 1989;143:529-530.

2. Committee on Infectious Diseases, American Academy of Pediatrics. *Red Book*. Elk Grove Village, Ill: American Academy of Pediatrics; 1988.

The Fallacy of the Hemorrhagic Shock and Encephalopathy Syndrome

Sir.—Chaves-Carballo et al¹ described nine infants with clinical features similar to heatstroke that they diagnosed as hemorrhagic shock and encephalopathy (HSE). An editorial in the same issue focuses on the inconsistencies and perplexities of the mysterious HSE syndrome.² During the past 15 years, I recall seeing several fatal cases that were presumptively diagnosed as either HSE or sudden infant death syndrome, but after an investigation of the home, could be diagnosed as heatstroke, exposure to toxic fumes, or both.^{3,4} In the cases diagnosed as heatstroke, based on on-site investigations, there was a lack of awareness by some pathologists that exposure of a young infant, like other small mammals, to high environmental temperatures may lead to cardiogenic shock and sudden death.⁵

Chaves-Carballo and coworkers¹ discussed the catastrophic clinical features and sparse laboratory data of HSE but failed to mention anything about the home environment of the young infants who were near death on arrival at the hospital. Similar to a death-scene investigation of infants presumed to have sudden infant death syndrome, questions may be asked concerning presumptive HSE cases. Were the cribs too close to the heat source? Did a defective heating system suddenly and unexpectedly deliver bursts of heat in the early hours during the winter or in the summer during a heat wave? Were the infants prescribed medication that prevented sweating? Was there inadvertent ingestion of cocaine or was the formula contaminated with phencyclidine hydrochloride? Were toxicologic tests, including a search for volatile hydrocarbons, performed

on the body fluids before prolonged resuscitative efforts were begun in the hospital?

Standard investigative procedure should be to encourage a thorough evaluation of the home environment from which a previously healthy infant is brought to the hospital and heatstroke is suspected. Information developed from scene investigation may help the physician to confirm a diagnosis of heatstroke and to prevent a similar occurrence. Like the forensic pathologist who may discard the presumptive and exclusionary diagnosis of sudden infant death syndrome for a more obvious cause following a death-scene investigation, the weak and misleading term HSE could be eliminated as a legitimate classification by pediatricians after a scene investigation provides evidence of heatstroke. Attempts to pinpoint elusive environmental hazards should be made only by personnel equipped to detect toxic agents in the ambient air and trained to uncover and document other useful information.

Although complete recovery is possible, the consequences of heat shock in infants who survive may include cerebral palsy, epilepsy, and mental retardation. Based on the potential savings in health care costs that could result from eliminating many of the indoor health hazards, an expanded effort is justified to train physicians in environmental medicine, including scene investigation.

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1. Chaves-Carballo E, Montes JE, Nelson WB, Chrenka BA. Hemorrhagic shock and encephalopathy: clinical definition of a catastrophic syndrome in infants. *AJDC*. 1990;144:1079-1082.

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Hyperpyrexia, Hemorrhagic Shock and Encephalopathy, and Creatinine Phosphokinase

Sir.—In his October 1990 editorial in *AJDC*, Corrigan¹ recommends that the "H" in the syndrome of hemorrhagic shock and encephalopathy (HSE) stand for hyperpyrexia. This is a welcome suggestion to the clinician because it underscores hyperpyrexia as an important clue to the diagnosis of this new syndrome. In February 1985, we were at a loss to explain a difficult patient who showed clinical symptoms of heatstroke. The original description of HSE by Levin et al² in 1983 did not view hyperpyrexia as a prominent feature of this disorder. Only two of the 10 patients described had temperatures of 41°C or greater. It was not until a subsequent report³ emphasized hyperpyrexia that we were alerted to the similarity between our case and those being described in the literature.

Patient Report.—A 3-year-old black girl was well until 11 PM on the evening of admission, when she vomited and had a seizure. The paramedics noted a temperature of 42°C and took her to a local hospital, where a temperature of 41.6°C was recorded and the seizure was stopped with phenobarbital sodium. On arrival at our hospital, the patient was markedly lethargic with occasional seizures. She had sharp disks and no focal neurologic signs. Her blood pressure was 76/40 mm Hg; pulse, 116 beats per minute; respiratory rate, 32/min; and she had normal general examination results. She was treated intravenously with fluids, cefuroxime sodium, gentamycin sulfate, and phenobarbital. Later, fresh frozen plasma, vitamin K, and blood were given. Results of admission laboratory tests showed a hemoglobin level of 123 g/L, white blood cell count of $20 \times 10^9/L$ (0.87 segmented neutrophils and 0.13 lymphocytes), and a platelet count of $350 \times 10^9/L$. The urine had 10 red blood cells per high-powered field. Serum electrolytes were normal with a carbon dioxide content of 15 mmol/L. The serum urea nitrogen was 8.9 mmol/L of urea, creatinine was 123.8 $\mu\text{mol/L}$, and aspartate aminotransferase was 185 U/L; blood ammonia, sugar, and calcium levels were normal. The cerebrospinal fluid was normal, and com-

puted tomographic scan of the head and chest roentgenogram were normal. Later, her hemoglobin level dropped to 70 g/L and her platelet count was $136 \times 10^9/L$. Her aspartate aminotransferase and alanine aminotransferase levels rose to 14 062 U/L and 6297 U/L, respectively, with repeated normal blood ammonia content. The γ -glutamyltranspeptidase level was 61 U/L, bilirubin level was 22.2 $\mu\text{mol/L}$, and serum protein levels were normal. Liver sonogram was negative. Partial thromboplastin time was 61 seconds (normal, 34 seconds), prothrombin time was 24 seconds (normal, 10.9 seconds), fibrin split products were positive, and the fibrinogen level was more than 4 g/L. The VDRL test had negative results. Serologic test results for hepatitis A and B, amebiasis, Epstein-Barr virus, and toxoplasmosis were negative. She had creatinine phosphokinase (CPK) levels that rose to 13 397 U/L. There was no myoglobinuria. Immunoglobulin levels were normal. Tests for urinary porphyrins, amino acids, and heavy metals had negative results. Results of hypnotic screening were negative. Multiple cultures for bacteria and viruses in the cerebrospinal fluid, blood, stool, and urine were negative. Two electroencephalograms showed diffuse slowing. Repeated cerebrospinal fluid and computed tomographic scans of the head were normal. The patient remained lethargic and febrile (around 39.4°C) for 8 days. She unexpectedly had a recurrence of fever and lethargy (although milder) from day 10 to day 17. Her laboratory values normalized by day 20. She was discharged on day 25, clinically well without neurologic sequelae.

Comment.—Since the original report by Levin et al² describing infants who died or had severe neurologic impairment, subsequent reports have enlarged the clinical spectrum of this syndrome. Hyperpyrexia is now frequently described, milder cases have been seen, and older children have been reported. Not every patient has met the criteria suggested by Levin et al and Chaves-Carballo et al⁴ to be diagnosed as having HSE. Nonetheless, the cases reported have unmistakable clinical similarities. Their resemblance to heatstroke, noted by several authors, was discussed in Corrigan's editorial.¹ The patient described here had a clinical profile of HSE in association with hyperpyrexia. The hyperpyrexia brought this new syndrome to our attention.

The markedly elevated CPK level (13 397 U/L) in this patient is note-

worthy since it is a common finding in heatstroke. In 34 patients with classic heatstroke reported by Tucker et al,⁵ for example, CPK elevations were observed in 75% of the cases. There are more than 160 reported cases of HSE, and the CPK levels were not recorded in most of these cases. In a few reports,^{4,6-8} markedly elevated CPK levels have been noted. Beaufils and Aujard⁶ had seven of seven patients with high CPK levels, and they expressed an interest in knowing these levels in the patients described by Levin et al. It would be interesting to know the CPK levels in all suspected cases of HSE. This information could be helpful in understanding these patients, and in strengthening the connection of heatstroke to the HSE syndrome.

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Hemorrhagic Shock and Encephalopathy: An Entity Similar to Heatstroke

Sir.—We read with interest the article by Chaves-Carballo et al¹ concerning the hemorrhagic shock and encephalopathy (HSE) syndrome. We recently cared for two infants with this entity² and we believe that the gastrointestinal tract is the source of this devastating illness. Approximately 74 infants and children with HSE have been described in the literature, most of whom presented with a prodromal illness consisting of vomiting and diarrhea.

The origin of HSE remains unexplained, but the multisystem failure seen in both HSE and heatstroke (HS) may be a final common pathway of an unexplained mediator. The hyperpyrexia may be the result of high metabolic requirements coupled with compensatory vasoconstriction. The shock state leads to increasing splanchnic vasoconstriction (which may actually be worsened by hyperpyrexia) that contributes to the release of these potentially toxic mediators. The vasoconstriction, caused by any combination of hypotension, hyperthermia, or gut ischemia, will allow leakage of endotoxin (lipopolysaccharide [LPS]) from the gastrointestinal tract. Lipopolysaccharide, in turn, may stimulate monokines, such as tumor necrosis factor. Leclerc et al³ described two infants with HSE with elevated tumor necrosis factor levels. Endotoxemia has been noted in heat-stressed animal models⁴ and may also play a role in HSE.

The gastrointestinal tract is a reservoir of endotoxin (LPS) and contains 1 mg of LPS per gram of feces.⁵ The mucosal barrier of the gut is easily disrupted by trauma, ischemia, hypoxia, hypotension, vasoactive agents, hyperthermia, and viral gastroenteritis.⁶ Lipopolysaccharide is usually sequestered by the reticuloendothelial cells (Kupffer cells) in the liver. The liver is very sensitive to heat stress, and autopsies have revealed abnormalities even in the early stages of HS.⁷ In patients with HSE the liver may not be able to handle the increased LPS burden. Lipopolysaccharide may alter vascular permeability, impair cell metabolism and oxygen utilization, initiate dis-

seminated intravascular coagulation, and produce hemodynamic changes resulting in hypotension, all of which are seen in both HS and HSE. Tumor necrosis factor has been demonstrated to mediate many of these changes as well. The pathologic features of HS and HSE are very similar, and we feel that cardiovascular failure, either primarily from the hyperthermia or perhaps secondary to the release of endotoxin, is the final pathway of these two entities.

The above discussion has clinical implications in that our patients² received fresh frozen plasma, which may have blocked the effects of LPS. Several of the patients described by Chaves-Carballo et al also received fresh frozen plasma, and it would be interesting to review the data of the survivors and see if any received fresh frozen plasma. Animal studies have recently shown that antibodies to LPS improve survival following HS.⁸ We need to evaluate more carefully the potential biochemical mediators of both HS and HSE. Levin et al⁹ noted elevated trypsin levels in 72% of their patients. These elevations are nonspecific findings and have been noted in hyperdynamic septic shock, adult respiratory distress syndrome, and pancreatitis.¹⁰ Deby-Dupont et al¹¹ have shown that there is a statistically significant correlation between high trypsin levels and septic phenomena. Many of the biochemical and physiological changes seen in HSE lead us to suspect that it is a "septic-mediated" process. Despite an extensive search, no organism has been implicated to date. It is hoped that the application of specific criteria for a diagnosis of HSE coupled with more extensive research will lead to a better outcome for these children.

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1. Chaves-Carballo E, Montes JE, Nelson B, Chrenka BA. Hemorrhagic shock and encephalopathy: clinical definition of a catastrophic syndrome in infants. *AJDC*. 1990;144:1079-1082.

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cephalopathy: is it really a new entity? *Pediatr Emerg Care*. 1990;6:131-134.

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The 'H' in Hemorrhagic Shock and Encephalopathy Syndrome

Sir.—I agree with the recent editorial by Corrigan¹ that hyperpyrexia is an important, striking element in the so-called hemorrhagic shock and encephalopathy syndrome. My experience with these patients has led me to conclude that the most striking features of this syndrome are the sudden onset of high fever, severe shock, and mental status changes in a previously healthy infant. The shock state is very impressive in that it requires almost unbelievable amounts of volume ex-

panders to reverse it, and occurs suddenly without any loss of extracellular fluid or blood from the body. Presumably this means that the shock is the result of massive third spacing in the gastrointestinal tract and/or massive vasodilatation. Both mechanisms suggest that a toxin is involved. It is my guess that this same, unidentified toxin affects skeletal muscle metabolism in such a way as to cause the hyperpyrexia. I agree with Corrigan¹ that a genetic predisposition (subclinical myopathy) may be required for this toxin to produce the full-blown syndrome.

Whittington et al² showed 5 years ago that if these patients were diagnosed early and the shock state reversed rapidly, all the other features of this syndrome were reversible. I have therefore concluded that all the other features of this syndrome are secondary to the shock and/or altered metabolic state of the patient (hyperpyrexia). Certainly, the "hemorrhagic" part of this disease is a minor secondary feature. As Corrigan suggests, this feature is most likely the result of some form of consumptive coagulopathy secondary to shock and/or toxin-induced damage of the endothelium. Hemorrhage plays no significant role in this syndrome. Even the encephalopathy may be a secondary feature of this syndrome caused by decreased cerebral perfusion or by endogenous toxins produced by the altered metabolic state. It is possible, however, that the toxin causing the syndrome may directly affect the brain and cause the encephalopathic features of this syndrome.

The name given to a syndrome is of great consequence. It may implicitly convey notions about the pathogenesis or pathophysiologic characteristics of the syndrome. As a result of my experience with this syndrome, I wrote more than 5 years ago that "the term 'hemorrhagic shock and encephalopathy syndrome' is misleading, because it may suggest that the shock is secondary to hemorrhage, which is conjecture. We propose that this entity simply be called 'shock and encephalopathy syndrome,' which describes the two main features and does not have implications for pathogenesis."² I would not, at this time, disagree with Corrigan's proposal that the syndrome be re-

named as the "hyperpyrexia, shock, and encephalopathy syndrome"¹ since hyperpyrexia is probably an important primary feature of this syndrome. I do, however, believe that our article should have been acknowledged in his editorial.

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1. Corrigan JJ Jr. The 'H' in hemorrhagic shock and encephalopathy syndrome should be 'hyperpyrexia.' *AJDC*. 1990;144:1077.

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Fetal Alcohol Syndrome: Misplaced Emphasis

Sir.—Little et al¹ seem to believe that "better communication" between the obstetric and pediatric staffs would somehow result in better diagnosis and treatment of infants with fetal alcohol syndrome (FAS). They do not seem to consider the dilemma of the pediatric clinician in this situation. The clinician is strictly bound first to do no harm. There has to be substantial benefit to justify telling the mother, "You damaged your child." As far as I can determine, since diagnosis is imprecise and judgmental, the relation between the phenotype and the behavior is highly variable, and specific treatment is nonexistent, there is little value in making the diagnosis of FAS.

What is imperative is the sophistication of obstetric services in supporting women during their pregnancies in a way that minimizes consumption of alcohol and other toxic substances and improves nutrition. It is also imperative that pediatricians develop widely available sophisticated services to support these mothers (and fathers) in caring for their children, whatever the degree and cause of their handicaps.

The clinical payoff comes in being sufficiently familiar with one's patients to be able to monitor various dysfunctional situations, including alcohol consumption. Only in the context of providing sufficient support for the family does this diagnosis have a decent chance of being beneficial.

Let us keep our eyes on the prize.

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1. Little BB, Snell LM, Rosenfeld CR, Gilstrap LC III, Gant NF. Failure to recognize fetal alcohol syndrome in newborn infants. *AJDC*. 1990;144:1142-1146.

In Reply.—We thank Dr Hess for commenting on our article. However, we believe that making the diagnosis of FAS is important because these are not simply growth-retarded infants. They are at high risk of having developmental abnormalities, some of which may be ameliorated by appropriate early intervention and occupational therapy. Accurate diagnosis of the syndrome may make a difference because the earlier the diagnosis is made, the sooner intervention and therapy may be implemented. We agree that caring for the mother during and after pregnancy is important. However, FAS may already be induced by the time a woman who drinks heavily realizes she is pregnant because organogenesis is frequently completed when the gravid state is recognized.

Hence, in the prevention of FAS, life-style practices of women of child-bearing age are the major issue, not obstetrical services rendered. We also agree that providing "widely available sophisticated services to support" parents is appropriate, but it is obvious that one must target certain services to specific needs. For example, early intervention needs of the mild to moderately mentally retarded child with FAS differ widely from those of a child with a congenital limb amputation.

Children with FAS should certainly be targeted for early intervention, and the earlier the diagnosis is made the greater the potential benefit.

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Herpes Zoster Oticus

Sir.—Herpes zoster oticus (HZO) is characterized by varicella zoster virus (VZV) infection of the ear in association with facial nerve palsy. It may result in permanent facial paralysis and denervation more frequently than does idiopathic Bell's palsy.¹ We describe three patients diagnosed with HZO associated with seventh cranial nerve palsy.

Patient Reports.—**PATIENT 1.**—A 10-year-old boy reported left ear pain for 4 days and progressive left facial weakness for 3 days before hospitalization. Otitis media had been diagnosed, and antimicrobial treatment had been initiated 7 days earlier. He had had chickenpox at age 4 years. Results of physical examination on admission revealed an afebrile child with infranuclear left facial paralysis. The left tympanic membrane was erythematous; vesicles were seen on the annulus of tympanic membrane and on the external auditory canal of the left ear. Intravenous acyclovir (30 mg/kg of body weight per day) was administered in three divided doses for 7 days. Vesicle cultures yielded VZV. The facial weakness partially resolved, and vesicles healed during the 7 days of therapy. Complete recovery ensued.

PATIENT 2.—An 18-year-old woman complained of pain on the left side of her neck for 8 days and weakness on the left side of her face for 7 days. The left side of her neck over the angle of the mandible, the left ear, and the surrounding area anteriorly were tender. The left pinna and external auditory canal were edematous with multiple vesicular lesions. She had a left infranuclear facial nerve weakness. She had had chickenpox at age 5 years. Cultures of the ear lesions yielded neither bacteria nor viruses. She received analgesic therapy, eye care, and acyclovir (22.5 mg/kg of body weight per day), which was administered intravenously for 4 days, followed by oral acyclovir (200 mg) four times a day for 6 days. Complete recovery ensued.

PATIENT 3.—A 9-year-old boy who had undergone cardiac transplantation 10 months earlier and who was receiving immunosuppressive therapy presented with a 2-day history of otalgia. On the day before admission, he developed a painful vesicular rash on his right ear. He had had chickenpox at age 5 years. On admission, he was afebrile and had infranuclear right facial palsy and vesicular lesions scattered over his right ear. Treatment with intravenous acyclovir (30 mg/kg of body weight per day) was initiated. Direct fluorescence antibody stain for VZV (Ortho Diagnostic Systems Inc, Raritan, NJ) and

a culture for VZV done before administration of acyclovir were both positive. He rapidly improved, with vesicular crusting and resolution of his facial palsy. After 3 days, therapy was changed to oral acyclovir (200 mg) four times a day for 7 days. At 6 months, the seventh nerve palsy had completely resolved.

Comment.—Facial palsy due to VZV infection is uncommon in children. May et al² reported 170 cases of facial palsy in subjects up to age 18 years, of which only four cases (2.4%) were associated with HZO.² In 1907, Ramsay-Hunt³ described a syndrome of herpesvirus infection involving the ear. Four types of HZO have been indentified: HZO without neurologic involvement; HZO with facial palsy; HZO with facial palsy and auditory symptoms; and HZO with facial palsy and both auditory and vestibular symptoms.

The clinical diagnosis of HZO rests on the combined presence of earache, cutaneous vesicles, and inflammation of the pinna, usually with ipsilateral facial weakness. Devriese and Moeskev,⁴ in a review of 102 patients with HZO, concluded that (1) in most cases, vesicles and weakness appear at the same time (in 25%, eruptions appear earlier); (2) the external ear has vesicles in 90% of patients; (3) maximal weakness usually occurs within a week; (4) complete paralysis is twice as common as incomplete paralysis; (5) recovery is better when appearance of vesicles precedes complete loss of function; and (6) 10% of patients with complete paralysis, and 66% with incomplete paralysis, recover totally. Clinical diagnosis can be confirmed by either viral culture or fluorescence antibody studies using VZV identification reagent (Fluorescein isothiocyanate-conjugated monoclonal anti-VZV; Ortho Diagnostic Systems Inc) on lesion specimens. Serologic studies are unlikely to be helpful in confirming the diagnosis. When performed, histologic examination of the facial nerve reveals scattered, diffuse, lymphocytic and plasma cell infiltrates and lymphocytic, perilymphatic, perivascular cuffing.^{5,6} This is in contrast to the typical edematous neuropathy with an acellular infiltrate seen in idiopathic Bell's palsy.⁷ The pathologic changes in facial nerve fibers in HZO are probably secondary to the involvement of Schwann cells by VZV.

The observed weakness may result from the inflammatory edema, which results in compression and ischemia of the facial nerve in its course through the narrow canal in the petrous bone.⁸

There are no standard recommendations for the management of HZO. Appropriate supportive therapy, including administration of analgesia and eye care, are indicated for all patients. Corticosteroids have been shown by some investigators to decrease pain during the acute phase, shorten the duration of facial weakness, and possibly decrease postherpetic pain, although the latter claim is controversial.⁹ Surgical intervention may be indicated in patients with normal prognostic and stimulation tests of the facial nerve, but with incomplete recovery.¹⁰ Acyclovir has been successfully employed, both orally and parenterally, for the treatment of VZV infections in both normal and immunocompromised hosts.¹¹⁻¹⁴ While prospective studies are lacking with respect to the specific effectiveness of acyclovir in treating HZO, our data and those of others¹⁵⁻¹⁷ support consideration of its use. Collaborative investigations are necessary before definitive therapeutic recommendations can be made.

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The authors would like to thank Diana Duke for her help in the preparation of this manuscript.

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Laparoscopic Cholecystectomy Under Continuous Epidural Anesthesia in Patients With Cystic Fibrosis

Sir.—Patients with cystic fibrosis often develop cholelithiasis. Subsequently, many will suffer from symptoms of their gallstones and develop cholecystitis. Because of the high

risks associated with induction of anesthesia in patients whose pulmonary status is compromised, surgery is sometimes delayed or avoided. With the advent of laparoscopic cholecystectomy and anesthetic techniques such as epidural blockade, another option is available that may be safe for many of these patients. I describe a patient whose surgical and anesthetic care was unique.

Patient Report.—An 18-year-old man with cystic fibrosis, severe recurrent pneumonia caused by *Pseudomonas aeruginosa*, and bronchiectasis was admitted to the Baptist Hospital of Miami (Fla) with worsening midepigastric pain, bilious vomiting, belching, and inability to eat. He had a 2- to 3-year history of biliary colic after eating certain foods. An ultrasound examination revealed multiple small gallstones in a contracted gallbladder; the gallbladder was not visualized after 4 hours of radionuclide scanning. His temperature was 102°F. He was emaciated and nonicteric. There were bilateral rales and rhonchi in all lung fields. Results of abdominal examination were unremarkable.

The white blood cell count was $26.7 \times 10^9/L$, with 0.75 segmented neutrophils and 0.11 banded neutrophils. This was higher than his usual level of $19 \times 10^9/L$ to $20 \times 10^9/L$. Serum amylase and bilirubin levels were normal. The glutamic oxaloacetic acid transaminase level was 93 U/L (normal range, 7 to 40 U/L), and the alkaline phosphatase level was 257 U/L (normal range, 22 to 125 U/L). A chest roentgenogram showed extensive bilateral changes consistent with cystic fibrosis. A pulmonary function test revealed severe obstructive ventilatory disease. His vital capacity was 1.98 L (51% of the predictive value). Forced expiratory volume in 1 second was 0.76 L (22% of the predictive value), and forced vital capacity was 1.81 L (48% of the predictive value).

Ceftazidime and tobramycin sulfate therapy was begun. Respiratory treatments were strictly enforced, including chest physiotherapy. He also received anhydrous theophylline, ipratropium bromide, and prednisone. Total parental nutrition (with intralipids) was started.

Six days after admission, a laparoscopic cholecystectomy under continuous epidural anesthesia was performed without complication. The umbilicus was infiltrated with 1% lidocaine hydrochloride (Xylocaine) prior to insufflating the abdomen with 2 L of carbon dioxide. A 10-mm trocar was placed in the umbilicus to accommodate the laparoscope, and, visualizing the peritoneal surface of the abdominal cavity, trocars were placed in the anterior axillary line (5 mm), midclavic-

ular line (5 mm), and midepigastrum (10 mm) just beneath the costal margin. The gallbladder was grasped through the 5-mm ports. Dissection, clip application, and electrocauterization were performed through the 10-mm epigastric port. A stone was lodged in the cystic duct, and removal caused a prompt backflow of bile. The common duct was small and normal. The gallbladder was dissected free from the liver bed, and the neck delivered through the umbilical port after placing the laparoscope in the midepigastrum. The gallbladder was decompressed with a small suction instrument and removed intact from the abdomen. The operation lasted 55 minutes. Cholecystitis and cholelithiasis were observed in the removed gallbladder by pathologic description. The patient was transferred to the intensive care unit overnight and was ambulatory in the unit most of the evening. The next morning, he was transferred to a room outside of the intensive care unit, and he was discharged from the hospital 5 days after surgery without complication or exacerbation of his pneumonia.

Comment.—As patients with cystic fibrosis live longer, their risk of developing cholelithiasis increases. Altered bile metabolism, malabsorption of bile acids, abundant mucoproteins, increased bile viscosity, and abnormalities of gallbladder emptying may promote biliary stasis and stone formation.¹ The diagnosis of symptomatic gallstones can be obscured because of the many other causes of abdominal pain in cystic fibrosis. Chronic antibiotic therapy for recurring pneumonia may mask the inflammation of cholecystitis.

The standard treatment for symptomatic cholelithiasis has been removal of the diseased gallbladder under general anesthesia with a subcostal incision. This is associated with the possibility of postoperative chest splinting and worsening pulmonary status. Cholecystectomy using a laparoscope causes lower morbidity and shorter hospital stays.² This procedure has been shown to be safe and effective in treating biliary diseases.³ In addition, use of continuous epidural anesthesia supplementing general endotracheal anesthesia has been reported for relief of postoperative pain in patients with cystic fibrosis.⁴

The procedure is usually performed under general endotracheal anesthesia. I have performed open cholecystectomies under continuous epidural anesthesia in elderly pa-

tients and in those patients refusing endotracheal intubation. In a motivated individual, it has not been difficult. Careful preoperative pulmonary function testing was performed almost routinely. The patients undergo surgery in a 30° to 40° sitting position, which is ideal for laparoscopy. This allows the liver to descend and expose the gallbladder. A 7- or 10-mm laparoscope is placed in the umbilicus. Below the costal margin, two 5-mm trocar punctures are made for grasping and manipulating the gallbladder, and a 10-mm trocar is used in the midepigastrium to dissect out and remove the gallbladder. Electrocautery was used in this instance for dissecting the gallbladder from the liver bed, but a laser could also be used. Cholangiograms can be obtained if necessary. Complications are minimal.

Laparoscopic cholecystectomy is a safe and effective treatment for patients with symptomatic gallstones. Patients with cystic fibrosis are at high risk of developing biliary colic and cholecystitis. Additional studies will be necessary to determine the risks and complications of performing this relatively new procedure on this select group of patients. The safety of continuous epidural anesthesia without endotracheal intubation cannot be determined by a single successful patient report, but it may be considered in patients with severe pulmonary disease.

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I thank Morton Schwartzmann, MD, for his help in the preparation of this report.

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War Souvenir Poisoning

Sir.—We recently had an alarming case of accidental atropine sulfate poisoning in a 4-year-old boy who was brought to the emergency department after injecting himself with 2 mg of atropine from a vacuum-loaded syringe. Why was such an article within reach of a young child? The boy's uncle had recently returned home from military service. He was stationed in Saudi Arabia and issued the syringe to use as an antidote in chemical warfare, ie, in case he suffered symptoms of cholinergic poisoning.

The child was observed for 24 hours after receiving two consecutive doses of activated charcoal.¹ He suffered only minor symptoms of tachycardia, mydriasis, and drying of the mucous membranes, and was released the following day. We were relieved that he had no complications, since, according to reports, people have died of anticholinergic poisoning.² In this case, the circumstances of the accident were more alarming than the symptoms. If troops continue to bring home these "souvenirs" to the United States, we will have to warn the families of military personnel about this sort of accident. Since the syringes are vacuum-loaded, a child can simply touch the needle tip of the device to be injected. Poisoning is likely with any curious child who has access to the syringe. We suspect this will not be the only case of atropine poisoning, and we urge other pediatricians to be aware of the possibility.

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Word Choice

Sir.—Wow! Eureka! It's magic! At least that is what Dr Hong says in his article in the September 1990 issue of *AJDC*.¹ He states: "... The phenomenological approaches have now been largely [do they have sizes?] abandoned..." and "... soon to be available through the magic of..."

Wow! What a change! Or were the alchemists correct in their hope that magic would create gold?

What a retrogression, really.

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In Reply.—Dr Gorlick apparently read my article with care and disagreed with my choice of words. Responding to his confusion, I could have sought refuge in my ethnicity. After all, when one is my age (sixtysomething) and harbors more than one language in his shrinking cerebral cortex, he ought to be entitled to a bit of poetic license. However, that would be a geriatric cop-out, so I consulted my dictionary.

Largely, used as an adverb, means "for the most part; mainly."^{1(p715)} Therefore, we can "largely" abandon a procedure without incurring the wrath of Strunk or White or any other protectors of the English language.

Magic, in addition to the common meanings (which include practices of alchemists), is defined as a "mysterious quality of enchantment."^{1(p753)} If Dr Gorlick has seen appreciation in the eyes of patients and their families after bringing comfort to their lives, he knows magic. If he has not, he is welcome to come and visit us. Gold from base metals he will not get, but magic he will surely experience.

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Saving Money With Home Care

Home care for children dependent on ventilators or other equipment is increasingly common. Until recently, such children remained in acute-care hospitals, using vast amounts of resources, even when they required less-than-acute care. Less than a decade ago, only a few demonstration projects in this country routinely attempted to return ventilator-dependent children to their homes and back into the community.¹ Today, an expanding home-care industry assists many established centers, pediatricians, and specialists in this transfer. The trend toward home care has been stimulated by rising societal expectations, awareness of the needs of the disabled, the increasing number of children rescued from formerly lethal conditions but sustaining disability in the process, and the high cost of inpatient care in acute-care facilities.

See also p 729.

Clearly, the foremost pressure is financial. Third-party payers, both public and private, do not believe they can sustain the high costs of maintaining such children in acute-care hospitals. The drain on hospital resources, once a few such children outlive their insurance coverage, can be devastating. There are two common institutional responses. Institutions faced with unsustainable expenses can devote efforts to shifting the cost to somebody else or to devising a cheaper way to provide quality care. Too many administrators are faithful followers of the first doctrinal response—"let the other guy pay." Meanwhile, others labor to achieve high-quality care in the home.

In this issue of *AJDC*, Fields et al² attempt to establish the level of cost-savings available to government agencies that endorse and fund home care for children disabled by respiratory conditions. Their findings make a fascinating and compelling argument. Forget the total costs to society, or the many advantages to the chil-

dren themselves. Maryland's Medicaid system saved itself almost \$80 000 per year per child by fully funding home care for these children. These savings were computed by comparing actual cost with estimates of the cost of care in a skilled-nursing facility. In states where the only option to home care is institutionalization in an acute-care hospital, potential savings are substantially higher.

The other striking finding of this report is the central role of the home nursing expenditure (68% of the total home care cost). Around-the-clock home nursing care for one of the patients described in the report cost Maryland \$135 000. While this still reflects a modest savings compared with institutionalization, the long-term success of the home care concept clearly depends on the rational and conservative use of this scarce resource.

Our program at The Children's Hospital of Alabama mandates a transitional period of 2 to 4 weeks in which home nurses are provided for as many hours per day as the patient's life depends on skilled care. While around-the-clock home nursing care during this period is common, some patients may receive considerably fewer hours of skilled care. After a successful transition to the home, the home nursing hours are reduced steadily to a level appropriate to each situation. This "appropriate level" depends largely on the availability and ability of family members to provide nursing care. Respite nursing care is also provided using the same concept. That is, sufficient skilled nursing care must be provided to enable the family to manage the remainder of the patient's care over the long term. Alternative approaches to the problem of providing skilled nursing care deserve further study. The use of nurse-extenders and direct payments to families for the skilled nursing care they provide may enable third-party payers to reduce expenditures for home nursing care, if this can be accomplished without sacrific-

ing safety or quality of care.

A recent article by Quint et al³ reminds us that the long-term impact of home care is still a subject of study and debate. Moving children from the hospital to the home for 5 to 10 years while we deplete the financial and emotional resources of their families will not benefit society or third-party payers. Establishing rational criteria for the use of home nursing care should be an important subject of future reports in this field because third-party payers will surely scrutinize this expense closely. Nevertheless, the work of Fields et al should help convince Medicaid agencies in other states to adopt waiver programs such as Maryland's.

I do not suggest that the cost-benefit equation is firmly resolved by these recent reports. Further studies of medical outcome, family impact, and psychosocial development are clearly needed. Because most centers are managing only a handful of patients, who have a wide variety of diseases and support requirements, it is difficult to formulate or evaluate generalizable hypotheses. Meticulous attention to the pathophysiologic characteristics of each case has been crucial to our efforts. As more centers report their results with various medical devices and with patients with varying diseases and medical requirements, a clearer view of the role of home care will emerge. Controlled trials are likely to be rare, and skeptical review will be as essential as ever.

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Buddy, Can You Paradigm?



George W. Brown, MD

George is our beloved, self-declared curmudgeon. He is a workhorse for AJDC, holding the record for most manuscripts refereed and for the shortest turnaround time of all of our reviewers. George provides in-depth comments designed to assist authors, whether the decision is to accept or reject the manuscript. Reading his comments is an education for all of us, not the least of whom are the authors. I have received a number of gracious comments concerning his reviews, and not all from authors whose work was accepted.

George also accompanies his reviews of manuscripts with comments for the editor—these are terse, always humorous, and intended to lighten what he believes is the “burden” of editorship. He comments on my local geography, flora and fauna, the travails of difficult judgments, and sundry other unrelated items. Occasionally, he sends me a cartoon, suitably modified for the editor’s lot. In each instance, these “bon mots” bring a smile to me and to those in our editorial group who have the pleasure of reading both his trenchant, on-the-mark reviews and the added fillip. He is not above punning, as the title of this month’s contribution clearly illustrates.

George has also contributed scholarly articles to AJDC and other journals on the statistical aspects of research and publication. George also is

very persnickety about correct language usage and mathematical expression. He points out small errors that occasionally creep into AJDC after escaping the eyes of the editors and others. He has even had the audacity to write a letter to the editor of the journal on which he serves as a board member! I guess he does qualify as a curmudgeon, even if it is his own designation, but to all of us at AJDC, he is a lovable one at that! We are most grateful for his hard work, good sense, and sense of humor. Long live curmudgeons like George.—V.A.F.

Kuhn¹ wrote that a paradigm is the constellation of beliefs, values, standards, and techniques shared by the members of a scientific community. The set of beliefs about classification of disability, impairment, or disease might be called a taxonomic or nosologic paradigm.

“Classification is a basic process man uses for ordering the universe, for simplifying a large amount of information through the placement of objects or events into definable subsets.”² Blashfield³ wrote: “Classification is a fundamental process in all sciences. A classification system contains the concepts which are the building blocks for a theory within that science.”

On the other hand, in his presidential address to the Society for Behavioral Pediatrics, Levine⁴ announced, “We are not invested in any disciplinary diagnostic system or catalog of diagnoses. We are . . . intellectually eclectic and liberated from a priori approaches. . . . We need not adhere over time to any fixed set of diagnostic instruments, systems of nosology, or therapeutic algorithms.”

The dismissal of formal classification closely followed publication of a report by Barkley⁵ reviewing DSM-III-R criteria for identifying attention deficit hyperactivity disorder and contrasting DSM-III-R criteria to criteria in the draft version of ICD = 10 = CM for identifying hyper-

kinetic disorders. Barkley et al⁶ also reported clinical studies showing that attention deficit disorder with hyperactivity is separable from attention deficit disorder without hyperactivity and that such diagnostic precision must, whenever possible, be included in child development classification systems.

Millon and Klerman⁷ edited a monograph in which some authorities defend DSM-III-R criteria while several others denounce it. The volume also discusses revisions that may appear in DSM-IV. The monograph explores the contempt expressed in some quarters toward “medical” classification schemes. For example, Eysenck⁸ describes DSM-III as “scientifically disastrous,” “anti-scientific and irrational,” and “empty, atheoretical, and antiexperimental.” According to Eysenck, it is the product of “the power structure of contemporary feudal baronetcies.”

A valuable contribution of valid classification systems to psychiatry, psychology, or developmental pediatrics would be improved prediction of outcomes of people assigned to particular diagnostic categories. Dawes et al⁹ documented that clinical judgments in the diagnosis and prediction of behavior are consistently inferior to actuarial (statistical) judgments about behavior. These authors warned that “Dismissing the scientific evidence or lamenting the lack of available methods will prove much less productive than taking on the needed work.”

The “needed work” is the development of a valid classification system along with a set of procedures to produce reliable and valid decisions about behavioral disturbances.

Faust and Ziskin¹⁰ present a devastating account of the poor reliability and validity of behavioral classification systems in legal and forensic environments. They show that classification of antisocial behavior is primitive and that “expert” prediction of violent criminal behavior is

about as valid as reading tea leaves or Tarot cards.

Developmental pediatrics is not the private preserve of pediatricians. Child development professionals pride themselves on their interdisciplinary methods; assessments and decisions are made by "teams" of expert participants. It gives us pause to recognize that there does not seem to be anything approaching a consensus in regard to classification of the disorders, the methods of assessment and diagnosis, the role of "theory" in nosology, generally accepted interventions, or prediction of outcomes for children with developmental problems.

Consensus fails both within and across disciplines—consider the needs of educators, language therapists, juvenile justice workers, the courts, and probation officers. Developmental pediatricians, neurologists, psychiatrists, and psychologists should be able to work together. Do they understand each other? Do they use a common language? Do they share paradigms? What about

the needs of the geneticist, sociologist, anthropologist, and epidemiologist in this ensemble?

Must we abandon hope for shared theories, models, standards? Where do we begin? Is *DSM-III* a reasonable starting place for building a consensus about classification and diagnosis? Must we throw it out, and begin with a new paradigm? Is the "medical model" obsolete? Should we adopt a doctrine that the "science" of child development can thrive without classification systems? When are we going to agree to "do the needed work"?

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Home Care Cost-effectiveness for Respiratory Technology-Dependent Children

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• We evaluated home care costs and the cost-effectiveness of home care vs alternative institutional care for respiratory technology-dependent children in a Medicaid Model Waiver Program. "Cost-savings" was measured as the difference between the established Medicaid reimbursable charges to enact an individualized care plan at a long-term care institution and the actual Medicaid reimbursements for home care. Ten patients—six dependent on mechanical ventilation and four with a tracheostomy who were receiving oxygen—were included in the analysis. The mean (\pm SD) annual home care costs were \$109 836 \pm \$20 781 for ventilator-dependent children and \$63 650 \pm \$12 350 for oxygen-dependent patients with a tracheostomy, representing annual savings of approximately \$79 000 per patient and \$83 000 per patient, respectively. The largest portion of home care reimbursements was for nursing care, accounting for 69.0% and 59.0% of the two patient groups. The full program (50 patients) has the potential for a savings of \$4 million per year.

(AJDC. 1991;145:729-733)

Home care for technology-dependent children is more cost-effective than institutional care.¹⁻⁵ Home care may save up to \$300 000 per year with mean costs of only 50% of institutional costs.¹⁻⁵ However, third-party payers frequently will not reimburse fully for the complete range

ten remain in short- and long-term care hospitals. In 1981, Congress enacted a law allowing transfer of public funding from hospital care to home care through the creation of a state Medicaid Home and Community-Based Waiver Program.⁶ Normally, by statute, the income and resources of parents living in the same household as their child are "deemed" available to the child. The crucial aspect of the Model Waiver Program is the waiving of "deeming of parental income," so that the child's income is the only consideration for financial eligibility. This resulted in the expansion of the Medicaid eligibility criteria to include middle- and upper-income families whose private insurance benefits either reached their maximum or would not reimburse for home care. Unfortunately, few physicians are aware of this program, few states have utilized it to its full extent, and there has been limited analysis of the program's cost-effectiveness.⁷

In 1985, the state of Maryland enacted a Medicaid Home and Community-Based Services Waiver Program for technology-dependent children, including those who are disabled by respiratory conditions and who require long-term mechanical ventilation or a tracheostomy and oxygen. Our purpose was to determine home care costs and the cost-effectiveness of home care vs alternative institutional care for respiratory technology-dependent children in this Medicaid Model Waiver Program.

PATIENTS AND METHODS

Data were collected by the Coordinating Center for Home and Community Care (CCHCC) in Maryland, a not-for-profit consortium of public and private institutions, agencies, and organizations that provided case management for children with respiratory disabilities at home or alternative living facilities. The CCHCC was a subcontractor to the Medicaid Model Waiver Program and was responsible for case management, monitoring the plan of care, and determining the cost-effectiveness of the program for each recipient. The CCHCC was initially funded in 1983 by a 3-year Special Program of Regional and National Significance (SPRANS) grant by the Bureau of Maternal and Child Health. The CCHCC is staffed with administrators, nurse case coordinators, educational coordinators, human service workers, a financial analyst, and a medical director.

All children in this analysis were Medicaid Model Waiver Program recipients who were discharged from short- and long-term care hospitals from April 1985 through June 1987. All patients required either mechanical ventilation or a tracheostomy and oxygen without mechanical ventilation, the need for which remained constant for the first year after hospital discharge, and

See also p 725.

of services required for home care, shifting the financial burden toward the family. Because many families are unable to dedicate the financial and personnel resources necessary for home care, technology-dependent children of-

Accepted for publication January 24, 1991.

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Presented in part at the 18th Annual Society of Critical Care Medicine Educational and Scientific Symposium, New Orleans, La, May 8, 1989.

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Table 1.—Annual Patient Data for Ventilator-Dependent Children

Diagnosis	Age at Discharge	Adjusted AIC*	Home Care Reimbursed†	Savings‡
Osteogenesis imperfecta	10 mo	186	116	70
Traumatic quadriplegia	9 y	210	143	67
Congenital heart disease tracheomalacia	14 mo	190	108	82
Central hypoventilation	4 y	194	80	114
Prune belly, hypoplastic lungs	3 y	200	98	102
Central hypoventilation	2 y	153	113	40
Mean ± SD§	. . .	188.9 ± 19.5	109.8 ± 20.8	79.1 ± 26.6

*Adjusted alternative institutional care (AIC) costs (in thousands of dollars) are estimates for care at the alternative institution after correction for actual, short-term rehospitalizations.

†Reimbursed home care costs (in thousands of dollars) are actual Medicaid reimbursements, including short-term hospital reimbursements.

‡Savings (in thousands of dollars) is adjusted AIC minus reimbursed home care.

§Means are based on raw data.

all of the first year's Medicaid reimbursable charges for home care were paid in full by July 1988.

To receive the Medicaid Model Waiver Program funding, Maryland State Regulations (COMAR 10.09.27—Home Care for Disabled Children Under a Model Waiver) required patients to be Maryland residents younger than 19 years of age and to meet medical, financial, and cost-effectiveness eligibility requirements.⁸ Medical eligibility was determined by a state-sanctioned, peer-review organization based on the primary care physician's assessment of medical conditions and care needs. Medical eligibility criteria specified in the regulations included disabilities requiring technological support. Financial eligibility required that parents apply for medical assistance for the child; only the child's income was considered when eligibility was determined. If the patient was financially and medically eligible, the cost-effectiveness of home care was evaluated. Specific care needs, including the amount of skilled nursing care, were individualized by a separate process (see below).

The cost-effectiveness eligibility was evaluated by comparing the projected costs of home care to the projected costs at an alternative care setting. The alternative care setting was defined as the least costly location capable of meeting the needs as prescribed in an individualized care plan (see below) and included pediatric long-term care facilities and short-term care hospitals. Pediatric long-term care hospitals in this region had in-house physicians 24 hours a day, while skilled nursing care facilities did not have such physician coverage. In this region, skilled nursing care facilities would not accept these children. For all patients in this analysis, the alternative care institutions were pediatric long-term care hospitals.

Annual costs for each patient's care at home or an alternative institutional setting were projected from an individualized care plan developed by a multidisciplinary team. This team consisted of specialty physicians, a primary care physician, parents, a group representing Maryland Medicaid (Children's Medical Services), a CCHCC representative (nurse coordinator), nursing agencies, and vendors. This plan detailed all foreseeable care for the next year, regardless of the medical setting, including nursing care, short-term hospital care, case management, outpatient care, medications, and other items, including durable medical equipment (eg, ventilators and apnea monitors), disposable medical supplies, transportation needs, adaptive equipment, and other therapies, such as occupational, physical, and speech therapies. The primary care physicians estimated the number of short-term care hospital admissions and the projected lengths of stay. For ventilator-dependent children, durable medical equipment and disposable medical supplies were estimated to account for 40% and 33% of the "other" category, respectively. For oxygen-dependent patients with a tracheostomy, these percentages were 29% and 42%, respectively. This care plan considered the patient's home environment and specific parental support needs. For example, the evaluation considered the number of caregivers in the home, the number and health of siblings, and

parental employment status (examples are available from the authors on request).

In this analysis, we used standard Medicaid methods to determine projected cost-effectiveness. A financial analyst from CCHCC computed the difference between the established Medicaid reimbursable charges (the Medicaid definition of "costs") at the alternative institution minus the Medicaid reimbursable charges for the same care plan at home. The costs of the projected short-term care hospital admissions were added to both the home care and alternative institutional computed expenses, as per Medicaid requirements. If the estimated costs of alternative institutional care exceeded the estimated costs of home care, the patient met the cost-effectiveness eligibility criteria. All calculations were reviewed by Medicaid before the release of funds.

Once home care was initiated, the multidisciplinary team evaluated the home care plan every 90 days to ensure that medical needs had not changed and that the cost-effectiveness of home care continued. If additional medical expenditures were necessary between the team meetings, they were evaluated by the financial analyst to ensure the continuation of cost-effectiveness before the funds were approved.

Savings by the program ("actual" cost-effectiveness) for the first year were calculated as estimated alternative institutional expenses minus home care reimbursements. Home care costs were calculated with use of actual Medicaid reimbursements and included the cost of case management. Home care nursing rates were reimbursed at \$18/h. Alternative institutional costs were estimated with use of Medicaid reimbursement rates (96% of charges) for care at the alternative institution, including ancillary charges. Three of the 10 patients assessed were hospitalized in the least costly alternative institution at the time of discharge, and their Medicaid reimbursements were used to confirm the accuracy of these projections. Because home care costs included reimbursements for short-term hospital care, alternative institutional cost estimates were also adjusted for these expenses, assuming an equal number of days of short-term hospital care for the alternative care institution as for home care. In addition, because nursing costs for home care depend on the number of days of home care, the projected nursing costs were adjusted for the actual number of short-term care rehospitalizations. Data are reported as mean ± SD.

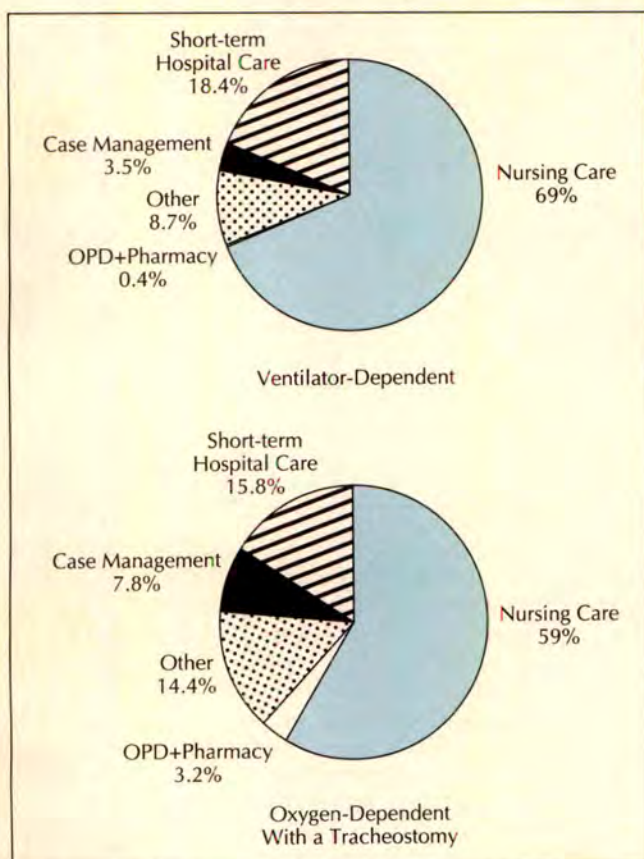
RESULTS

Ten patients—six dependent on mechanical ventilation (Table 1) and four with a tracheostomy and receiving oxygen (Table 2)—were included in our analysis. The mean cost of home care for ventilator-dependent children was \$109 836 ± \$20 781 per patient for the first year. The estimated cost of alternative institutional care was \$188 909 ± \$19 472 per patient, for an estimated annual savings of \$79 074 ± \$26 558 per patient. The mean cost of home care for the four oxygen-dependent patients with a

Table 2.—Annual Patient Data for Oxygen-Dependent Children With a Tracheostomy*

Diagnosis	Age at Discharge	Adjusted AIC	Home Care Reimbursed	Savings
Bronchopulmonary dysplasia	1.5 y	118	66	52
Partial trisomy 1, mental retardation with cerebral palsy	10 mo	177	71	106
Congenital heart disease, tracheomalacia	2.5 y	147	46	101
Congenital heart disease, Down syndrome	5 y	146	72	74
Mean \pm SD	...	146.8 \pm 24.0	63.6 \pm 12.4	83.2 \pm 25.0

*See Table 1 footnotes for additional information.



Distribution of annual home care reimbursements for ventilator-dependent and oxygen-dependent children with a tracheostomy in the Medicaid Model Waiver Program. Short-term hospital care includes all reimbursements for rehospitalizations for the first year after discharge; OPD includes physician visits and outpatient hospital charges; and includes other, durable medical equipment, disposable medical supplies, transportation, and occupational, physical, and speech therapies.

tracheostomy was \$63 650 \pm \$12 350 per patient for the first year, while the estimated cost of alternative institutional care was \$146 836 \pm \$23 992 per patient, resulting in an estimated annual savings of \$83 187 \pm \$25 028 per patient.

Components of home care costs for the first year appear in the Figure. For ventilator-dependent patients, nursing care accounted for 69.0% of total costs; short-term hospital care, 18.4%; case management, 3.5%; outpatient costs, 0.3%; and pharmacy, 0.1%; the remaining expenses, including durable medical equipment, disposable medical supplies, occupational and physical therapies, and transportation, accounted for 8.7%. For oxygen-dependent children with a tracheostomy, nursing care accounted for 59.0% of the total costs; short-term hospital care, 15.8%; case management, 7.8%; outpatient care, 2.4%; and phar-

macy, 0.8%; the remaining items averaged 14.2%.

Nursing care accounted for more than half of the reimbursements in both groups (Figure). Multidisciplinary team evaluations after the first 90 days at home decreased nursing care for three ventilator-dependent children (Table 3) and one oxygen-dependent child who had a tracheostomy (Table 4), as parents were able to provide more care. Projected nursing requirements did not increase for any child.

The mean reimbursements for nursing care for the first year were substantially lower than were projected from the individualized care plan. Only one patient in each group actually required more nursing care than projected from the initial care plan and quarterly reviews. These increases resulted from the provision of extra nursing care in lieu of rehospitalization for acute illness. The projected cost of home care nursing for ventilator-dependent children was \$94 704 \pm \$41 381 per patient, while their reimbursements for nursing care were \$74 916 \pm \$36 508 per patient (Table 3). The difference of \$19 788 \pm \$21 732 per patient represents 21% of all ordered nursing care that remained unfilled. The projected costs of home care nursing for oxygen-dependent children with a tracheostomy was \$51 102 \pm \$20 183 per patient, while their reimbursements for nursing care were \$37 848 \pm \$6397 per patient (Table 4). The difference of \$13 254 \pm \$17 419 per patient represents 26% of all ordered nursing care that remained unfilled.

COMMENT

Medicaid is the major public funding source for medical services to people with disabilities. Previously, few state Medicaid programs reimbursed for the full range of services needed by technology-dependent children in non-hospital settings. The Omnibus Reconciliation Act of 1981 (Public Law 97-35) expanded eligibility for Medicaid benefits in two major ways. First, it granted eligibility for benefits to finance medical and nonmedical support services and the purchase of equipment to be used in the home, such as mechanical ventilators and skilled nursing care. These services and equipment usually are not covered by Medicaid, frequently requiring Medicaid recipients to remain in a more costly institutional setting. Second, this waiver enables only the child's income to be considered for financial eligibility, expanding the Medicaid eligibility criteria to include middle- and upper-income families whose private insurance benefits either "capped out" or would not reimburse for home care. President Reagan applied this waiver to Katie Beckett, a 5-year-old girl in Iowa, who was ventilator-dependent after contracting encephalitis, to allow Medicaid funding for home care. "Katie Beckett" waivers had to be individually approved by the Health Care Financing Administration (HCFA). In 1982, a Medicaid Home and Community-Based Waiver Program

Table 3.—Annual Home Care Nursing Requirements in Ventilator-Dependent Children

Patient	Nursing Care*		Projected Reimbursement	Actual Reimbursement†	Savings§
	Discharge	90 d-1 y			
1	16/7	16/7	103	95	8
2	24/7	24/7	158	135	23
3	24/7	16/7	105	49	56
4	19/5	16/2	43	53	-10
5	16/7	16/7	105	81	24
6	16/7	8/7	54	36	18
Mean ± SD	94.7 ± 41.3	74.9 ± 36.5	19.8 ± 21.7

*Ordered from the individualized care plan. Data are hours per day/days per week.

†Projected reimbursement (in thousands of dollars) are the computed costs to fulfill the ordered nursing care (columns 2 and 3) corrected for actual short-term rehospitalizations.

‡Actual reimbursements (in thousands of dollars) as paid by Medicaid for home care nursing.

§Savings (in thousands of dollars) is projected reimbursements minus actual reimbursements.

||Means are based on raw data.

Table 4.—Annual Home Care Nursing Requirements in Oxygen-Dependent Children With a Tracheostomy*

Patient	Nursing Care*		Projected Reimbursement	Actual Reimbursement	Savings
	Discharge	90 d-1 y			
1	9/6	9/6	50	45	5
2	16/7	8/5	51	33	18
3	6/5	6/5	27	32	-5
4	12/7	12/7	77	41	36
Mean ± SD	51.1 ± 20.2	37.8 ± 6.4	13.2 ± 17.4

*See Table 3 footnotes for additional information.

(formerly known as the "Model Waiver") was developed, allowing each state to establish a program for up to 50 blind or disabled children and adults who, in the absence of community services, would require long-term institutional care. The Health Care Financing Administration approved the Medicaid Home and Community-Based Services Waiver Program and expanded the eligible population to include up to 50 technology-dependent children per state, removing the necessity of applying to the Health Care Financing Administration for approval for each child.

The Medicaid Model Waiver Program instituted in Maryland has produced substantial cost savings for the payer. The mean annual home care costs were \$109 836 for a ventilator-dependent child and \$63 650 for an oxygen-dependent child with a tracheostomy. These home care costs for ventilator-dependent children are comparable with those reported by Frates et al.² The estimated annual savings of approximately \$79 000 for each ventilator-dependent child and \$83 000 for each oxygen-dependent child with a tracheostomy were computed with use of individualized home care plans. Our computations for cost savings may be more reliable than those previously reported, because this Medicaid system reimbursed for almost all (96%) long-term care institutional charges, and care needs were individualized for each child. Other studies compared home care costs with average short-term care hospital costs³ or simply the minimal daily rate charged by short- or long-term care hospitals.^{2,4}

Both medical and social needs are important in determining home care supports. Children with similar technology and care requirements may be discharged with very different amounts of professional caregiver support,⁵ because discharge planning attempts to provide for the

family's needs. The parents of all these patients were technically competent to provide all required home care nursing. However, the number of hours they were able to provide these services was dependent on their own medical and psychosocial needs. Some parents and other siblings had illnesses and disabilities, and financial considerations required some parents to work outside the home. Frequent reassessments and the flexibility to adjust to changing medical status or unanticipated social conditions will help to ensure a successful home care program.

Actual home care reimbursements for nursing care were considerably less than projected (Tables 3 and 4). For 80% of the patients, the major component of this difference was unutilized nursing care secondary to a lack of available skilled nursing care. For the remaining 20% of patients (one in each group), nursing care reimbursements were greater than projected from their individualized care plan, as these two patients were provided with additional nursing care in lieu of rehospitalization for acute illness. Overall, annual nursing care reimbursements averaged approximately \$20 000 per patient less than ordered for ventilator-dependent children and \$13 000 per patient less than ordered for oxygen-dependent children with a tracheostomy, equivalent to 21% and 26% of the ordered nursing care hours, respectively. This problem has increased in proportion to the number of children discharged home. Coupled with the existing nursing shortage, maintaining appropriate nurse staffing for children receiving home care may become even more difficult as this patient population continues to increase.

A more complete cost-effectiveness analysis would include other direct and indirect costs, considerations of patient benefits, and quality of outcomes.^{9,10} Other costs of home care borne by parents include home remodeling,

increased utility charges, lost income from work, transportation, child care, and training of families and personnel. "Out-of-pocket" expenses are a major cause of stress to the family.¹¹ Items such as lost family leisure time were not considered. Although the lack of inclusion of direct and indirect costs may have resulted in an overestimation of cost savings, several of these additional costs (eg, transportation and child care) could have been a factor if the child was in the alternative institution. In addition, use of the least costly institution (long-term care institutions) as the alternative to home care often underestimated the alternative institutional costs, because long-term care beds for technology-dependent children were frequently unavailable at the time of hospital discharge. Long delays in patient discharges to long-term care institutions in this region were routine. Therefore, many patients would have remained in more costly short-term care facilities for longer periods. With the approximate Medicaid reimbursements of \$1000 to \$1200 per day for these patients in short-term care hospitals in this region, savings for home care compared with short-term hospital care was approximately \$250 000 to \$300 000 per year.

The degree to which health services are covered and reimbursed by a state's Medicaid rules affect the setting and the amount of care a technology-dependent child receives. Although these methods could be applied to other states, cost-effectiveness would depend on Medicaid reimbursements for acute care for each individual state. In addition, if Medicaid reimbursements to hospitals for ventilator-dependent children are meager, the financial incentives of resultant savings for a home care program are nonexistent.¹²

In summary, the Medicaid Model Waiver Program is highly cost-effective for the state of Maryland, with approximate mean savings of \$79 000 per year for each ventilator-dependent patient and \$83 000 per year for each oxygen-dependent patient with a tracheostomy. The full program (50 patients) has the potential to save \$4 million per year and allows greater availability of specialized short- and long-term care beds. Although we believe that decisions concerning resource allocations should depend on patients' needs and be proportional to expected ben-

efits, lack of access to financing is a real barrier to appropriate home care. The savings from home care of some individuals also could be used to offset the losses from others, allowing the aggregate costs to remain less costly than alternative institutional care.

This work was supported, in part, by a grant from the US Department of Health and Human Services, Bureau of Maternal and Child Health, through its Special Projects of Regional and National Significance (SPRANS).

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A Comparative Trial of the Reactogenicity and Immunogenicity of Takeda Acellular Pertussis Vaccine Combined With Tetanus and Diphtheria Toxoids

Outcome in 3- to 8-Month-Old Infants, 9- to 23-Month-Old Infants and Children, and 24- to 30-Month-Old Children

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● The reactogenicity and immunogenicity of the Takeda acellular pertussis vaccine combined with tetanus and diphtheria toxoids were compared in 139 infants aged 3 to 8 months, 60 infants and children aged 9 to 23 months, and 99 children aged 24 to 30 months. Good antibody responses to pertussis toxin (PT), filamentous hemagglutinin (FHA), and agglutinogens occurred in all age groups after both the third and fourth doses. After the fourth (booster) dose, the mean antibody values in initially seronegative infants vaccinated at 3 to 8 months of age were as follows: anti-PT, 67.8 enzyme-linked immunosorbent assay units (EU) per milliliter; anti-FHA, 149.5 EU/mL; the agglutinin titer was 125.6. The values in initially seronegative children vaccinated at 24 to 30 months of age were as follows: anti-PT, 92.9 EU/mL; anti-FHA, 251.7 EU/mL; the agglutinin titer was 275.8. Reactions following immunization were minimal. Except for drowsiness after the first dose in infants, there were no clinically significant differences in reactions between infants and older children. The findings in this study coupled with the recent demonstration of efficacy of this vaccine in 2-year-old children supports the recent Japanese recommendation to lower the age of immunization with acellular pertussis vaccine combined with tetanus and diphtheria toxoids to 3 months.

(AJDC. 1991;145:734-741)

Accepted for publication November 12, 1990.

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In Japan, since the fall of 1981, children have been vaccinated against pertussis exclusively with acellular pertussis vaccines.¹⁻⁵ Until recently, diphtheria-tetanus-

See also pp 746 and 750.

pertussis immunization with adsorbed vaccines containing acellular pertussis components (APDT) routinely commenced at about 2 years of age in Japan, and over 40 million doses of vaccine have been administered. Currently, epidemic pertussis is controlled in Japan, but the incidence of the disease is higher in infants than it was in the early 1970s, when diphtheria-tetanus-pertussis vaccines containing whole-cell pertussis antigens were used and immunization commenced at 3 months of age. Today, the majority of cases of pertussis in Japan occur in nonimmunized children who are younger than 2 years.⁶

This communication reports the results of a field trial with a single lot of commercially available APDT from Takeda Chemical Industries Ltd (Osaka, Japan). The study was done as a cooperative Japan-United States effort by Takeda and Lederle Biologicals, Pearl River, NY. It was designed to supply information for both the Japanese and US acellular pertussis vaccination programs.

Although the Japanese acellular pertussis vaccination program has been highly successful, it has become evident that a lowering of the age of immunization is necessary to reduce the occurrence of pertussis in infants. This report compares the reactogenicity and immunogenicity of APDT in 3- to 8-month-old infants, 9- to 23-month-old infants and children, and 2-year-old children. The results of this study should provide valuable information for the United States as well as for Japan. Since pertussis is currently well controlled in the United States through the use of whole-cell vaccines, it would be exceedingly difficult to do an efficacy trial with an acellular pertussis vaccine.

Table 1.—Antibody Responses to PT, FHA, and Agglutinogens in Vaccinated Infants and Children With Negative Preimmunization Antibody Values*

Time	Age at Immunization, mo	No.	Geometric Mean Titer (95% CI)		
			Anti-PT, EU/mL	Anti-FHA, EU/mL	Agglutinin Titer
Before first vaccination	3-8	107	1.4 (1.3-1.5)	2.7 (2.4-3.0)	<10.0 (. . .)
	9-23	57	1.1 (1.0-1.2)	2.2 (1.9-2.6)	<10.0 (. . .)
	24-30	82	1.1 (1.1-1.2)	2.2 (1.9-2.5)	<10.0 (. . .)
Before third vaccination	3-8	87	51.0 (43.8-59.4)	49.3 (43.0-56.7)	69.8 (54.2-90.0)
	9-23	52	54.4 (45.8-64.5)	61.0 (50.0-74.4)] †	86.7 (66.6-112.9)
	24-30	67	45.0 (38.7-52.3)	45.6 (38.7-53.7)]	101.5 (81.6-126.2)
After third vaccination	3-8	101	74.5 (66.6-83.4)	110.3 (96.9-125.5)	156.7 (125.5-195.7)] †
	9-23	55	74.6 (63.9-87.1)	114.9 (96.9-136.1)	159.7 (128.4-198.6)] †
	24-30	77	74.9 (66.4-88.9)	107.1 (90.3-127.0)	225.2 (185.8-272.9)] †
Before booster shot	3-8	79	13.1 (11.3-15.2)] †	20.9 (17.6-24.9)] † ‡	22.0 (17.9-27.1)
	9-23	28	18.8 (14.3-24.7)]	32.2 (24.6-42.1)]	34.8 (24.5-49.5)
	24-30	54	19.0 (15.3-23.6)]	40.5 (30.2-54.4)]	37.0 (26.1-52.5)
After booster shot	3-8	79	67.8 (58.4-78.8)] † †	149.5 (126.5-176.7)] † ‡	125.6 (94.3-167.3)] † ‡
	9-23	27	105.4 (77.9-142.6)] †	274.2 (210.7-357.0)] †	318.7 (225.9-449.7)] †
	24-30	52	92.9 (75.0-115.1)]	251.7 (204.0-309.2)]	275.8 (194.6-390.9)]

*PT indicates pertussis toxin; FHA, filamentous hemagglutinin; and CI, confidence interval. Negative preimmunization antibody values were less than 10 enzyme-linked immunosorbent assay units (EU) per milliliter of anti-PT antibody, less than 10 EU/mL of anti-FHA antibody, and an agglutinin titer less than 10. The agglutinin titer is expressed as the reciprocal of the serum dilution. Extremely low concentration in most samples made calculation of the value before the first geometric mean titer impractical, and accordingly significance testing was not performed.

† $P < .05$, Tukey's Studentized Range Test, comparison between age groups at specific times.

‡ $P < .01$.

Table 2.—Seroconversion Rates (%) in Vaccinated Infants and Children With Negative Preimmunization Antibody Values*

Time	Age at Immunization, mo	No.	Anti-PT, EU/mL			Anti-FHA, EU/mL			Agglutinin Titer		
			≥10	≥20	≥40	≥10	≥20	≥40	≥10	≥40	≥160
Before third vaccination	3-8	87	98.9	94.3	65.5	100.0	93.1	60.9	92.0	74.7	33.3
	9-23	52	100.0	98.1	69.2	98.1	96.2	73.1	96.2	88.5	‡ 36.5
	24-30	67	98.5	94.0	59.7	100.0	94.0	52.2	98.5	92.5	40.3
After third vaccination	3-8	101	100.0	98.0	88.1	100.0	100.0	96.0] †	99.0	93.1	64.1] †
	9-23	55	100.0	100.0	94.6	100.0	98.1	96.4]	100.0	96.4	63.6]
	24-30	77	100.0	97.4	81.8	100.0	100.0	87.0]	100.0	97.4	81.8]
Before booster shot	3-8	79	72.2	29.1] †	6.3	86.1	51.9] †	20.3] †	79.8	33.0	7.6
	9-23	28	78.6	42.9]	10.7	92.9	78.6]	46.4] †	‡ 96.4	53.6	3.6
	24-30	54	77.8	50.0	18.5	96.3	70.4	46.3]	92.6	50.0	13.0
After booster shot	3-8	79	98.8	96.2	79.8	100.0	100.0	96.2	100.0	82.3] †	48.1] †
	9-23	27	100.0	96.3	92.6	100.0	100.0	100.0	100.0	100.0] †	‡ 81.5] †
	24-30	52	98.1	96.2	88.5	100.0	100.0	100.0	98.1	98.1]	73.1]

*PT indicates pertussis toxin; EU, enzyme-linked immunosorbent assay unit; and FHA, filamentous hemagglutinin. For negative preimmunization antibody values, see Table 1.

† $P < .05$, Tukey's Studentized Range Test, comparison between age groups at specific times.

‡ $P < .01$.

However, since the efficacy of Takeda's APDT vaccine in children 2 years of age or older has been demonstrated in a large household contact study in Japan,⁷ the present study in Japan might provide important data that could serve as a surrogate for predicting efficacy in young infants.

SUBJECTS AND METHODS

Subjects

The study participants were healthy 3- to 30-month-old infants and children at the time of the first dose of APDT. They had neither been immunized previously with pertussis-containing

vaccines nor had a history of pertussislike illness. At enrollment, the details of the study were explained to the parents or guardians, and verbal informed consent was obtained.

The vaccine was administered by the deep subcutaneous route in a volume of 0.5 mL per dose. Following the initial immunization, the children received two subsequent doses of vaccine at 6- to 10-week intervals, and a fourth dose was given 12 to 18 months after the third dose. Serum samples for antibody determination were obtained before the first inoculation and immediately before and 1 month after both the third dose and the booster (fourth) dose.

Table 3.—Antibody Responses to PT, FHA, and Agglutinogens in Vaccinated Infants and Children With Positive Preimmunization Antibody Values*

Time	Age at Immunization, mo	No.	Geometric Mean Titer (95% CI)		
			Anti-PT, EU/mL	Anti-FHA, EU/mL	Agglutinin Titer
Before first vaccination	3-8	32	5.3 (3.8-7.5)	10.2 (7.9-13.1)	10.7 (10.0-11.4)
	24-30	17	2.3 (1.0-5.2)	12.5 (8.7-18.1)	10.2 (9.8-10.7)
Before third vaccination	3-8	32	56.6 (47.3-67.9)	63.0† (54.5-72.3)	65.1 (45.0-94.1)
	24-30	16	48.7 (27.5-86.2)	150.5‡ (90.9-249.2)	97.3 (51.3-184.6)
After third vaccination	3-8	28	77.5 (65.2-91.9)	108.7 (88.9-132.8)	157.2 (102.1-242.3)
	24-30	16	107.5 (64.3-179.6)	223.6§ (150.6-332.0)	255.9 (149.4-438.3)
Before booster shot	3-8	26	18.7 (13.8-25.3)	24.6 (18.1-33.3)	18.9 (14.1-25.4)
	24-30	10	16.6 (9.3-29.5)	34.5 (20.7-57.5)	41.4 (27.4-62.6)
After booster shot	3-8	25	62.7 (50.3-78.3)	162.1 (127.5-206.0)	102.7 (71.7-147.0)
	24-30	11	149.4 (65.3-341.9)	242.6 (174.1-337.3)	159.8 (69.9-365.6)

*For abbreviations, see footnotes to Table 1. The agglutinin titer is expressed as the reciprocal of the serum dilution. Positive preimmunization antibody values were 10 EU/mL or greater of anti-PT or anti-FHA antibody or an agglutinin titer of 10 or greater.

†P = .02 when compared with a similar value in infants with negative preimmunization antibody values (Table 1).

‡P = .0001.

§P = .002.

Table 4.—Antibody Responses to PT, FHA, and Agglutinogens in 3- to 8-Month-Old Infants With Negative Preimmunization Antibody Values*

Time	Age at Immunization, mo	No.	Geometric Mean Titer (95% CI)		
			Anti-PT, EU/mL	Anti-FHA, EU/mL	Agglutinin Titer
Before first vaccination	3	35	1.6 (1.4-1.9)	2.8 (2.2-3.4)	<10 (. . .)
	4-5	28	1.4 (1.1-1.7)	2.7 (2.1-3.4)	<10 (. . .)
	6-8	44	1.2 (1.1-1.4)	2.7 (2.3-3.2)	<10 (. . .)
Before third vaccination	3	32	48.8 (35.7-66.9)	50.1 (37.9-66.2)	56.5 (37.3-85.6)
	4-5	22	53.1 (42.5-66.4)	46.5 (35.4-61.0)	75.1 (41.8-134.9)
	6-8	33	51.7 (40.6-65.9)	50.61 (41.6-61.6)	87.7 (54.6-122.2)
After third vaccination	3	35	69.6 (56.8-85.3)	97.7 (77.2-123.6)	118.8 (79.5-177.7)
	4-5	25	77.4 (62.6-95.7)	115.4 (89.1-149.4)	173.9 (110.2-274.5)
	6-8	41	77.3 (64.0-93.2)	118.9 (97.0-145.8)	186.3 (132.5-261.9)
Before booster shot	3	31	11.5 (9.1-14.4)	20.5 (15.3-27.5)	14.1 (11.8-16.9)
	4-5	23	13.1 (10.0-17.2)	21.3 (15.7-29.1)	20.6 (14.7-28.8)
	6-8	25	15.5 (11.4-21.0)	21.1 (15.1-29.5)	40.6 (25.4-64.8)
After booster shot	3	30	51.6 (40.8-64.2)	116.4 (88.5-152.9)	70.4 (47.8-103.7)
	4-5	23	70.4 (54.3-91.3)	165.7 (116.8-235.0)	139.6 (84.4-230.9)
	6-8	26	90.1 (68.8-118.0)	182.5 (140.7-236.6)	223.3 (127.6-390.5)

*For abbreviations and explanation of values, see footnotes to Table 1.

†P < .05, Tukey's Studentized Range Test, comparison between age groups at specific times.

‡P < .01.

After each immunization, the child was observed in the clinic for local and systemic symptoms for 30 minutes. Thereafter, clinical follow-up was performed by the parents or guardians. Specific observations were made 3 and 6 hours after immunization and then daily for 7 days. The following were monitored: axillary temperature; the presence or absence of fretfulness, drowsiness, anorexia, and vomiting; and local reactions. Pain and warmth at the immunization site were graded as marked (2+), present (+), or none (-). Redness and swelling were quantified as 5 cm or greater (2+), 1 to 4 cm (+), and 0 to less than 1 cm (-); induration was evaluated as clearly palpable (2+), slightly palpable (+), and none (-).

Vaccine

The adsorbed APDT vaccine used in this trial was a single lot (HJ027) of a commercially available Japanese vaccine manufactured by Takeda Chemical Industries Ltd. It contained 25 Lf/mL

of diphtheria toxoid and 3.5 Lf/mL of tetanus toxoid. The pertussis component was made up of three main antigens: filamentous hemagglutinin (FHA), lymphocytosis-promoting factor hemagglutinin (LPF), which is also called pertussis toxin (PT), and agglutinogens, in an approximate ratio of 90:9:1. In addition, it has been found that the pertussis component contains a 69-kD outer-membrane protein that has protective efficacy in animal studies.⁸

Laboratory Studies

All serologic tests except for anti-69-kD studies were performed by Takeda Chemical Industries Ltd with supervision by the Japanese National Institute of Health. Agglutinating antibodies were determined by the method of Sato et al,⁹ and antibodies to PT and FHA were determined by an indirect enzyme-linked immunosorbent assay.^{9,10} Antibodies to 69-kD outer membrane protein were determined in a subset of serum samples by

Table 5.—Antibody Responses to Diphtheria and Tetanus Toxoids in Vaccinated Infants and Children*

Time	Age at Immunization, mo	Diphtheria Antitoxin, IU/mL		Tetanus Antitoxin, IU/mL	
		No.	GMT (95% CI)	No.	GMT (95% CI)
Before first vaccination	3-8	16	<0.01 (. . .)	16	<0.01 (. . .)
	9-23	22	<0.01 (. . .)	31	<0.01 (. . .)
	24-30	19	<0.01 (. . .)	18	<0.01 (. . .)
Before third vaccination	3-8	16	0.8 (0.6-1.0)	16	1.2 (0.8-1.7)
	9-23	22	0.5 (0.3-0.7)	29	1.1 (0.8-1.5)
	24-30	19	0.7 (0.5-0.9)	18	1.5 (1.0-2.1)
After third vaccination	3-8	16	1.6 (1.2-2.1)	16	2.0 (1.5-2.8)
	9-23	22	1.5 (1.1-2.0)	31	2.1 (1.6-2.8)
	24-30	19	1.7 (1.4-2.1)	17	2.6 (1.9-3.4)
Before booster shot	3-8	45	0.3 (0.2-0.4)	45	0.2 (0.1-0.2)] †
	9-23	21	0.3 (0.3-0.4)	21	0.4 (0.3-0.7)]
	24-30	34	0.3 (0.2-0.4)	34	0.2 (0.1-0.3)
After booster shot	3-8	45	6.7 (4.9-9.2)	45	3.1 (2.4-4.1)
	9-23	21	10.2 (7.2-14.5)	21	4.9 (3.6-6.7)
	24-30	34	8.3 (6.2-11.1)	34	4.3 (3.4-5.4)

*GMT indicates geometric mean titer; CI, confidence interval.

†P<.01, Tukey's Studentized Range Test, comparison between age groups at specific times.

Table 6.—Incidence (%) of Adverse Reactions in Vaccinated Infants and Children*

		Within 24 Hours of				1-7 Days After			
	Age at Immunization, mo	First Vaccination	Second Vaccination	Third Vaccination	Booster Vaccination	First Vaccination	Second Vaccination	Third Vaccination	Booster Vaccination
Any	3-8	36.3	42.9	52.2	64.7	6.6	11.0	6.6	7.8
adverse reactions	9-23	28.3	40.2	44.2	66.7	9.8	5.4	3.5	10.3
	24-30	38.1	54.8	50.8	64.0	13.8	4.8	4.0	10.7
Systemic reaction	3-8	20.9	16.2	15.6	21.6	3.9	6.7	3.9	7.8
	9-23	13.0	10.9	10.5	18.0	4.4	4.4	4.7	5.1
	24-30	14.4	12.1	10.7	22.7	8.8	6.4	3.3	12.0
Local reactions (+/2+)	3-8	20.3	35.0	47.5	57.8	4.0	7.8	3.4	5.2
	9-23	20.2	34.8] †	43.5	64.1	7.9	3.3	1.2	7.7
	24-30	28.6	50.8] †	48.0	60.0	10.3	3.2	2.4	9.3
Local reaction (2+)	3-8	2.3	7.2	7.3	19.0	1.7	1.1	3.4	11.2
	9-23	1.1	6.5	5.9	28.2	6.7	1.1	1.2	10.3
	24-30	0.8	7.9	13.0	30.7	5.6	1.6	6.5	8.0

*Local reactions were graded as marked (2+), present (+), or none (-).

†P<.05, Tukey's Studentized Range Test.

enzyme-linked immunosorbent assay at Lederle Biologicals by a previously described method.¹¹ All agglutinin titers are expressed as reciprocals of the serum dilution. Antitoxins to diphtheria and tetanus toxins were measured by the microcell culture method using VERO cells¹² and by passive hemagglutinations using tetanus toxoid-coated sheep erythrocytes,¹³ respectively.

Statistical Evaluation

The geometric mean titers and their 95% confidence intervals were computed based on the log assay values at baseline and those before and after the third immunization. These values were first logarithmically transformed, then the (simple) means and 95% confidence intervals were computed, and finally the means and confidence intervals were expressed as the antilogarithms. Comparisons across age groups are based on a nonparametric version of Tukey's Studentized Range Test. Differences among the groups were reported as statistically significant if a two-sided P value of .05 or less was obtained.

The clinical reactions were classified into those observed within

the first 24 hours and those observed between 24 hours and 7 days after injection. Clinical reactions observed among different age groups of children were analyzed using Tukey's Studentized Range Test.

Participants

A total of 454 infants and children originally entered the study. Of this group, there were four subjects under 3 months of age, 182 who were 3 to 8 months old, 92 who were 9 to 23 months old, 126 who were 24 to 30 months old, and 50 who were older than 30 months of age. Clinical reactions in subjects 3 to 30 months of age were analyzed. One hundred two children did not receive their subsequent immunizations in the allotted periods and therefore were excluded from analysis.

There were a total of 298 infants and children 3 to 30 months old immunized according to the protocol. Of this group, 246 had prevaccination antibody values that were considered negative (ie, less than 10 enzyme-linked immunosorbent assay units [EU] per milliliter of anti-PT antibody, less than 10 EU/mL of anti-FHA

Table 7.—Incidence (%) of Specific Systemic Reactions in Vaccinated Infants and Children

	Age at Immunization, mo	Within 24 Hours of				1-7 Days After			
		First Vaccination	Second Vaccination	Third Vaccination	Booster Vaccination	First Vaccination	Second Vaccination	Third Vaccination	Booster Vaccination
Temperature									
$\geq 37.5^{\circ}\text{C}$	3-8	5.5	4.2	4.5	2.7	3.6	8.4	7.0	11.5
	9-23	4.6	3.3	9.9	8.1	6.8	10.0	4.9	10.8
	24-30	2.6	0.9	4.5	9.9	7.0	8.0	5.4	9.9
$\geq 38.5^{\circ}\text{C}$	3-8	0.0	0.0	1.3	0.9	1.8	0.6	1.3	6.2
	9-23	1.1	1.1	0.0	2.7	2.3	2.2	4.9	2.7
	24-30	0.9	0.0	0.0	0.0	4.4	3.5	2.7	4.2
Fretfulness	3-8	9.3	10.1	8.4	8.8	3.3	2.2	2.8	3.5
	9-23	5.4	5.5	4.7	10.3	3.3	3.3	3.5	2.6
	24-30	7.2	4.8	5.7	8.0	6.4	6.4	2.5	5.3
Drowsiness	3-8	17.1	7.8	8.9	8.8	3.3	3.4	0.0	3.5
	9-23	8.7*	4.4	5.9	7.7	1.1	3.3	2.4	5.1
	24-30	8.0	8.1	8.2	6.7	2.4	2.4	0.8	1.3
Anorexia	3-8	3.3	2.2	3.9	7.0	3.3	4.5	3.3	7.0
	9-23	2.2	1.1	2.4	5.1	2.2	2.2	3.5	5.1
	24-30	4.0	2.4	4.9	6.7	8.8	4.8	2.5	8.0
Vomiting	3-8	0.6	2.2	1.1	0.0	1.1	3.4	1.1	3.5
	9-23	2.2	1.1	1.2	0.0	1.1	0.0	1.2	0.0
	24-30	0.0	0.0	0.0	0.0	3.2	2.4	0.0	4.0

* $P < .05$, Tukey's Studentized Range Test, comparison between age groups at specific times.

antibody, and an agglutinin titer less than 10), and 52 had one or more positive prevaccination antibody values (ie, ≥ 10 EU/mL of anti-PT or anti-FHA antibody, and an agglutinin titer of ≥ 10). Data from these participants were used for the analysis. There were 107 infants 3 to 8 months old, 57 infants and children 9 to 23 months old, and 82 children 24 to 30 months old with negative preimmunization values, and 32 infants 3 to 8 months old, three infants and children 9 to 23 months old, and 17 children 24 to 30 months old with positive preimmunization values. To evaluate the immunogenicity and reactogenicity of the vaccine in a homogeneous population, it was decided that the most appropriate major analysis would involve only those subjects with negative preimmunization values. Antitoxins to diphtheria and tetanus toxins were measured in serum samples from 57 and 65 vaccinees, respectively. Some of the children in each age group returned for their booster (fourth dose) immunization, and their prebooster and postbooster antibody values were determined.

RESULTS

Serologic Responses

The serum antibody responses to PT, FHA, and agglutinogens in the immunized infants and children with negative preimmunization values are presented in Table 1. Following two doses of vaccine, the mean values of the antibodies to all three antigens were significantly higher than those before vaccination in all three age groups. There were no significant differences in responses to PT or FHA among the three age groups after two doses except that the anti-FHA antibody values in the infants and children immunized at 9 to 23 months of age were higher than those in the children immunized at 24 to 30 months of age. Following the third immunization, the values of the antibodies to the respective antigens significantly increased further in all three vaccination age groups. The increases were approximately 1.5-fold for anti-PT values and two-fold for anti-FHA values and for agglutinin titers. The only

significant difference between the immunized infants and younger children (3 to 23 months old) and the older children was related to agglutinin titers. The agglutinin geometric mean titer after the third dose was 156.7 in 3- to 8-month-old infants, 159.7 in 9- to 23-month-old infants and children, and 225.2 in 24- to 30-month-old children.

Marked decreases in anti-PT and anti-FHA values and agglutinin titers were observed in the samples taken before the booster dose. Greater decreases were observed in children who had received the first dose when they were 3 to 8 months of age. High antibody values and titers were observed in serum samples taken 4 weeks after the booster dose. The responses after the booster in the infants immunized at 3 to 8 months of age were relatively low compared with those immunized at the other ages.

In Table 2, the percentage of children with negative preimmunization antibody values who obtained selected antibody titers following immunization is presented. After the third immunization, the respective values of those immunized at 3 to 8 months of age with an antibody level of 40 EU/mL or greater against PT and against FHA and an agglutinin titer of 40 or greater were 88%, 96%, and 93%; the respective values in those immunized at 9 to 23 months of age were 95%, 96%, and 96%, and the respective values in those immunized at 24 to 30 months of age were 82%, 87%, and 97%.

Presented in Table 3 are the antibody responses in vaccinated infants (3 to 8 months old) and children (24 to 30 months old) with a positive preimmunization antibody value to one of the three vaccine antigens (PT, FHA, or agglutinogens). When compared with the antibody values in infants and children with negative preimmunization values (Table 1), it is noted that those with positive preimmunization antibody values had higher antibody values

Table 8.—Incidence (%) of Specific Local Reactions in Vaccinated Infants and Children*

		Within 24 Hours of				1-7 Days After			
	Age at Immunization, mo	First Vaccination	Second Vaccination	Third Vaccination	Booster Vaccination	First Vaccination	Second Vaccination	Third Vaccination	Booster Vaccination
Pain									
+ / 2 +	3-8	3.4	3.3	4.6	14.4	0.0	0.6	1.1	2.7
	9-23	6.8	11.1	11.9	37.5	0.0	0.0	1.2	3.0
	24-30	9.5	18.7	18.2	24.7	1.6	1.6	0.8	4.1
2 +	3-8	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	9-23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	24-30	0.0	0.0	0.0	2.7	0.0	0.0	0.0	0.0
Warmth									
+ / 2 +	3-8	5.1	10.7	12.1	30.4	1.7	2.8	1.7	1.8
	9-23	3.4	13.2	19.1	53.1	3.4	1.1	2.4	6.1
	24-30	3.2	21.0	29.4	37.0	4.8	4.0	1.7	8.2
2 +	3-8	0.6	0.0	0.6	5.4	0.6	0.0	0.0	0.9
	9-23	0.0	2.2	0.0	12.5	0.0	0.0	1.2	3.0
	24-30	0.8	0.8	0.0	4.1	0.0	0.0	0.0	2.7
Redness									
+ / 2 +	3-8	18.3	26.4	42.4	53.5	3.4	5.0	3.9	3.5
	9-23	14.6	28.6	35.7	61.5	5.6	4.4	1.2	7.7
	24-30	17.5	41.3	43.1	53.3	8.7	4.0	2.4	6.7
2 +	3-8	1.1	4.5	3.4	11.2	0.0	0.0	1.7	10.3
	9-23	0.0	2.2	3.6	18.0	2.3	2.2	1.2	7.7
	24-30	0.0	5.6	8.1	22.7	1.6	1.6	5.7	10.7
Swelling									
+ / 2 +	3-8	8.0	18.0	33.9	47.4	2.3	2.8	2.3	4.3
	9-23	9.0	23.1	27.4	56.4	5.6	3.3	1.2	10.3
	24-30	7.1	28.6	38.2	50.7	7.1	3.2	3.3	6.7
2 +	3-8	0.6	2.8	5.1	12.1	0.0	0.0	2.3	8.6
	9-23	0.0	2.2	3.6	20.5	2.3	0.0	1.2	10.3
	24-30	0.0	4.0	8.1	20.0	0.8	0.0	4.1	9.3
Induration									
+ / 2 +	3-8	5.8	19.7	25.4	40.5	5.1	6.7	5.1	7.8
	9-23	9.0	22.0	28.6	47.4	12.4	5.5	7.1	10.3
	24-30	7.9	27.8	33.3	41.3	13.5	4.0	4.1	9.3
2 +	3-8	0.6	3.9	4.5	13.8	1.1	1.1	1.7	6.9
	9-23	1.1	5.5	1.2	18.4	5.6	1.1	1.2	7.7
	24-30	0.0	6.4	8.9	22.7	5.6	0.0	3.3	1.3

*Reactions were graded as marked (2+), present (+), or none (-).

†P<.01, Tukey's Studentized Range Test, comparison of age groups at specific times.

‡P<.05.

against PT and FHA in the following specimens: before the third immunization, anti-FHA in both the 3- to 8-month-old and the 24- to 30-month-old groups; after the third immunization, anti-FHA in the 24- to 30-month-old group; and before the booster, anti-PT in the 3- to 8-month-old group.

The mean serum antibody responses to PT, FHA, and agglutinogens in infants with negative preimmunization antibody values immunized at 3 months, 4 to 5 months, and 6 to 8 months are presented in Table 4. The following antibody responses in 3-month-old infants were less than those in 6- to 8-month-old infants: agglutinin titers before and after the booster dose and anti-PT values after the booster.

Following the third dose of vaccine, the serum samples from 23 infants 3 to 8 months of age at the time of im-

munization had a 69-kd antibody value of 150 EU/mL. Twenty-three children initially vaccinated at 24 to 30 months of age had a value of 138 EU/mL.

Table 5 gives the antibody responses to diphtheria and tetanus toxoids. Following two doses of vaccine, mean antitoxin levels against diphtheria and tetanus toxins in all age groups were much greater than established protective levels (0.01 IU/mL) for each antitoxin.

Clinical Reactions

During the first 24 hours after the first immunization, between 28% and 38% of the vaccinated individuals had one or more reaction complaints (Table 6). The specific complaints during the first 24 hours and between 24 hours and 7 days after immunization by age group and vaccine

dose are presented in Tables 7 and 8, respectively. Fever within the first 24 hours after immunization occurred in less than 10% and fever during the next 7 days occurred in less than 12% of the vaccinated subjects. Drowsiness was notably more common after the first dose in 3- to 8-month-old infants than with any other dose in infants or children. Local reactions tended to increase in incidence and severity with each dose regardless of age. Pain and local warmth within the first 24 hours became increasingly more common after the second, third, and booster doses. Frequencies of local redness and swelling, both mild and severe, within the first 48 hours were significantly greater after the booster dose than after any of the primary injections in all three age groups. No serious side effects such as encephalopathy or convulsions were observed.

COMMENT

In Japan, there are six manufacturers of acellular pertussis vaccines, including Takeda Chemical Industries Ltd. The acellular pertussis vaccines are divided into two types, the T type and the B type. T-Type vaccines contain predominately FHA, varying amounts of PT and 69-kd protein, and small amounts of agglutinogens. B-Type vaccines, on the other hand, contain only PT and FHA.

This study and a specific efficacy trial were planned in 1986. At that time, there were no formal efficacy data for any of the six individual APDT vaccines in use in Japan, but it was clear that collectively they were effective in controlling pertussis in children 2 years of age and older. It was reasoned that the demonstration of similar antibody patterns in infants and older children would support the use of the Takeda APDT vaccine in infants.

In 1986, an efficacy trial with two acellular vaccines was under way in Sweden, and that study has subsequently been completed.¹⁴ In the Swedish trial, two different vaccines were used. One vaccine, a two-component product, contained equal amounts of PT and FHA (B-type vaccine) and the other vaccine contained only PT. Two doses of both vaccines produced good antibody responses to the vaccine antigens. It was anticipated that the results from the Swedish trial would provide efficacy data for older infants (>6 months of age) and, more importantly, might reveal FHA and/or PT antibody levels that correlated with protection in vaccinees.

The results of the Swedish trial revealed that both vaccines were efficacious in preventing the manifestations of severe pertussis, but when mild cases of pertussis were included, the calculated efficacy was less than expected. Furthermore, it was found that the vaccinees in whom pertussis developed had postimmunization antibody levels to PT that were similar to those in vaccinees who did not get pertussis.

The Takeda vaccine used in this trial is a T-type vaccine and is different from the two vaccines used in Sweden. Specifically, the Takeda vaccine contains agglutinogens as well as PT and FHA. In addition, this vaccine also contains the recently identified 69-kd outer-membrane protein.^{8,15,16} Antibodies to this protein occur following natural pertussis and after immunization with whole-cell pertussis vaccines and have had protective efficacy in animal studies.^{11,15,16}

In the present trial, reactions following immunization were minimal. Except for the occurrence of drowsiness, which was most common after the first dose in infants,

there were no clinically significant differences in reactions between the infants and the older children.

In the present trial, the infants and children with negative preimmunization antibody values had good antibody responses to the four antigens studied (Table 1). In general, the 24- to 30-month-old children had more vigorous responses than the 3- to 8-month-old infants. Specifically, after the third dose, the agglutinin titer was 156.7 in 3- to 8-month-old infants and 225.2 in the 24- to 30-month-old children ($P < .05$). After the booster dose, the antibody values for all three antigens were significantly greater in the older children. However, the values in the infants vaccinated at 3 to 8 months of age were comparable with those observed after natural pertussis in Japanese infants.¹⁷

When we analyzed infants and children who had preimmunization values for PT or FHA above 10 EU/mL or an agglutinin titer greater than or equal to 10 (positive preimmunization antibody values), the results were not considerably different from those in vaccinees with negative preimmunization values (Tables 1 and 3). Those with positive preimmunization antibody values in a few instances had better responses than those vaccinees with negative preimmunization values. With whole-cell pertussis vaccines, it has been noted in the past that in 2-month-old infants the antibody response is blunted by the presence of high antibody values in the preimmunization serum samples.¹⁸ In a recent study, Savage et al¹⁹ reconfirmed this finding with a whole-cell pertussis vaccine but found that vaccinees responded equally well with regard to anti-PT antibody when immunized with an acellular vaccine regardless of the preimmunization antibody value.

In the present study, the positive preimmunization antibody values were in most instances probably due to previous unrecognized infections rather than to the presence of transplacentally acquired maternal antibody. Savage and associates¹⁹ found that most infants had no detectable antibody to PT and FHA by the age of 4 months. In our study, only a small number of infants were less than 4 months old.

When the 3- to 8-month-old immunization group is analyzed further by age (Table 4), it is noted that, in general, those vaccinated at 3 months of age had lower antibody values at all follow-up points than the infants vaccinated at the older ages. Since by study design the infants in each age group had low preimmunization antibody values, it would seem that this age-related difference in immune response may not be due to transplacentally acquired maternal antibody but instead may be associated with age-related immunologic development. In a trial in the United States with an APDT vaccine with the Takeda acellular pertussis component, immunization was initiated at 2 months of age.²⁰ Although it is difficult to compare immune responses in two studies in two countries in which the laboratory tests were performed in the respective countries, it appears that the US children vaccinated at 2 months of age had lower antibody values to PT, FHA, and agglutinins than the Japanese children in whom immunization commenced at 3 months of age. Except for the response to agglutinins, these differences were not great. However, even after adjustment for laboratory differences, the agglutinin response in the US children was significantly less than that in the Japanese children.

The cause of this difference is unknown, but three possibilities need to be considered. First, it may be due to the maturity of the immune system (ie, 2 vs 3 months of age). Second, it could be due to a genetic difference between the two populations. Third, it could be due to the route of vaccine administration (ie, deep subcutaneous vs intramuscular). In Japan, vaccine is administered with a longer needle than used in the United States and it is injected at a narrow angle so that the vaccine enters subcutaneous tissue. In the United States, vaccine is injected directly into a muscle mass.

It is reassuring to note that antibody to the 69-kd protein was similar after the third dose in both those vaccinated as infants and those over 2 years of age at the time of immunization. Also, in the large study in the United States, infants vaccinated with the Takeda pertussis vaccine had 69-kd antibody values similar to those of whole-cell vaccine recipients after the third and fourth vaccine doses.²⁰

The efficacy of the Takeda APDT vaccine has recently been demonstrated in 2-year-old children in Japan.⁷ In a household contact study with 62 Takeda APDT-vaccinated children and 62 unvaccinated children, the efficacy was found to be 98% for the prevention of typical pertussis and 81% for the prevention of mild possible pertussis and typical pertussis combined.

At present, the specific serum antibody values, types, or combinations that confer protection against pertussis after immunization are not known. However, the antibody findings in the present study in association with the efficacy data in 2-year-old children are encouraging and lead us to suggest that the Takeda APDT vaccine may be effective in infants.

Recently, a three-community epidemiologic study in Japan was presented.²¹ In this study, the incidence of pertussis in two communities where immunization commenced at 2 years of age was compared with that in an area in which immunization was begun at 3 to 6 months of age. The observation period was 2 years. The incidence of pertussis in the community in which 3- to 6-month-old infants were immunized was less than one third of that in the other two communities, where vaccination was started at 2 years of age. In these communities, vaccines of several different manufacturers were used, suggesting efficacy in infants with T-type vaccines.

In December 1988, the Ministry of Health and Welfare in Japan recommended that the initiation of vaccination with APDT be lowered from 2 years to 3 months of age. The results of the present study lend support to this recommendation.

This study was supported by Lederle Laboratories.

This study was abstracted in part in *Tokai J Exp Clin Med*. 1988;13(suppl):15-19.

We are indebted to Takeda Chemical Industries Ltd for assistance in making arrangements for the study.

We also acknowledge Denise Tritt for her technical assistance.

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Dose-Related Immunogenicity of *Haemophilus influenzae* Type b Capsular Polysaccharide–*Neisseria meningitidis* Outer Membrane Protein Conjugate Vaccine

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● We studied the immunologic responsiveness to *Haemophilus influenzae* type b capsular polysaccharide–*Neisseria meningitidis* group b outer membrane protein conjugate vaccine (PRP-NOMP) in children 2 to 42 months of age with vaccine dosages containing 7.5, 15, or 30 µg of PRP. Overall, PRP-NOMP was highly immunogenic. Geometric mean titers of anti-PRP antibody increased from 0.09 to 3.3 mg/L and 6.6 mg/L following each dose of vaccine, respectively, in the 2- to 18-month age group. Similarly, anti-PRP antibody geometric mean titers increased from 0.12 to 5.9 mg/L in the older than 18-month age group. However, we noted an apparent inverse relationship between vaccine dosages and immune responses following two doses of PRP-NOMP in 2- to 18-month-old children. Anti-PRP antibody geometric mean titers were 12.0, 6.9, and 3.5 mg/L, respectively, after the second dose of vaccine containing 7.5, 15, or 30 µg of PRP. Additional studies are needed to understand the mechanisms responsible for this inverse relationship and also to determine the optimal dosage of PRP-NOMP for young children.

(AJDC. 1991;145:742-745)

The variable immunogenicity^{1,2} and efficacy³⁻⁶ of the *Haemophilus influenzae* type b capsular polysaccharide vaccines (polyribitylribitol phosphate [PRP]) has prompted the continued development of PRP–protein conjugated vaccines. One such vaccine utilizes the outer membrane protein complex of *Neisseria meningitidis* group b covalently linked to PRP (Ped-vax-HIB; Merck Sharp & Dohme Research Laboratories, West Point, Pa). Previous studies of *H influenzae* type b capsular polysaccharide–*N meningitidis* group b outer membrane protein conjugate vaccine (PRP-NOMP) utilizing dosages ranging from 7 to 15 µg of PRP have shown im-

proved immunogenicity in children as young as 2 months of age when compared with PRP vaccines.⁷⁻¹¹ We undertook a study to determine the effect of varying vaccine dosages on the immunogenicity of PRP-NOMP.

PATIENTS AND METHODS

Vaccine

Each vial of a lyophilized PRP-NOMP vaccine consisted of 30.7 µg of PRP, 334 µg of partially purified outer membrane protein of *N meningitidis* (NOMP), and 4.1 mg of lactose. A single lot of vaccine (lot 1072/C-P298/37359) was utilized and reconstituted with the appropriate amount of aluminum hydroxide containing diluent (0.45 mg/mL) to provide 7.5 µg of PRP and 82 µg of NOMP, 15 µg of PRP and 163 µg of NOMP, or 30 µg of PRP and 326 µg of NOMP and 0.5-mL dose.

Study Design

Informed consent was obtained from the parents of 2- to 42-month-old children presenting to the General Pediatric Clinic at the Childrens Hospital of Los Angeles (Calif) following guidelines established by the Committee on Clinical Investigations at Childrens Hospital of Los Angeles. Children 2 to 18 months of age received two doses of 7.5 µg of PRP and 82 µg of NOMP, 15 µg of PRP and 163 µg of NOMP, or 30 µg of PRP and 326 µg of NOMP intramuscularly during a 2-month andiod, while children older than 18 months of age received a single dose of 7.5 µg of PRP and 82 µg of NOMP, 15 µg of PRP and 163 µg of NOMP, or 30 µg of PRP and 326 µg of NOMP according to a predetermined randomization.

Safety and tolerability were assessed by parental observation for temperature and local or systemic complaints (swelling, erythema, or tenderness at injection site; excessive crying; appearing tired or irritable; and diarrhea or vomiting) 5 days following immunization. Parents were also asked to record any clinical complaints on a standard report form. All forms were returned to the investigators, and a telephone follow-up interview was obtained when appropriate.

Serology

Serum was collected from children aged 2 to 18 months before each dose of vaccine and 1 month following the second dose of vaccine. Children aged 19 months or older underwent phlebotomy before and 1 month following immunization. Serum was stored at –70°C, and anti-PRP antibody levels were determined by radioimmunoassay¹² in a "blinded" fashion.

Statistical Analysis

All antibody values were converted to logarithms for statistical comparisons. Anti-PRP levels below the lower limit of our assay

Accepted for publication January 10, 1991.

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Table 1.—Comparison of Geometric Mean Anti-PRP Antibody Concentrations Before and After Immunization With *Haemophilus influenzae* Type b—*Neisseria meningitidis* Outer Membrane Protein Conjugate Vaccine Among 2- to 18-Month-Old Children Who Received 7.5, 15, or 30 µg of PRP*

Vaccine Dose, µg (No.)	Mean ± SD Age, mo†	Prevaccination, mg/L‡	After First Injection		After Second Injection	
			Mean ± SD Interval, wkt	Antibody Levels, mg/L‡	Mean ± SD Interval, wkt	Antibody Levels, mg/L‡
7.5 (22)	8.8±5.1	0.09 (0.07-0.14)	8.5±1.3	4.1 (2.4-7.1)	5.0±1.6	12.0 (6.1-24)
15 (22)	7.3±3.8	0.08 (0.06-0.10)	8.2±0.9	2.8 (1.3-6.0)	5.1±1.5	6.9 (3.6-13)
30 (22)	7.8±4.6	0.09 (0.06-0.13)	8.3±1.0	3.1 (1.8-5.4)	4.7±1.2	3.5 (2.3-5.4)

*PRP indicates polyribitylribitol phosphate. Values in parentheses are 95% confidence intervals.

†No significant difference by analysis of variance.

‡Significantly different ($P=.021$) by analysis of variance.

Table 2.—Comparison of Geometric Mean Anti-PRP Antibody Concentrations Before and After Immunization With *Haemophilus influenzae* Type b—*Neisseria meningitidis* Outer Membrane Protein Conjugate Vaccine Among 19- to 42-Month-Old Children Who Received 7.5, 15, or 30 µg of PRP*

Vaccine Dose, µg (No.)	Mean ± SD Age, mo†	Prevaccination, mg/L‡	Mean ± SD Interval, wkt	Antibody Levels, mg/L‡
7.5 (15)	23.5±6.3	0.14 (0.10-0.22)	4.4±1.1	6.2 (2.9-13.4)
15 (21)	28.4±3.7	0.10 (0.07-0.14)	5.1±2.0	4.9 (3.0-8.1)
30 (13)	28.2±5.7	0.12 (0.06-0.25)	5.0±1.7	7.3 (4.1-13.0)

*PRP indicates polyribitylribitol phosphate. Values in parentheses are 95% confidence intervals.

†No significant difference by analysis of variance.

(<0.12 mg/L) were assigned a value of 0.06 mg/L when calculating geometric mean titers (GMTs). Comparisons of anti-PRP antibody GMTs were performed with analysis of variance or Student's t test¹³ where appropriate.

RESULTS

Patient Characteristics

Of the 115 children enrolled in the study, 66 (57%) were 2 to 18 months of age (mean±SD, 8.0±4.5 months), while 49 (43%) were 19 to 42 months of age (26.9±5.5 months). In the 2- to 18-month age group, 22 each received 7.5 µg of PRP and 82 µg of NOMP (seven aged 2 to 4 months, three aged 5 to 7 months, five aged 8 to 11 months, and six aged 12 to 17 months), 15 µg of PRP and 163 µg of NOMP (six aged 2 to 4 months, seven aged 5 to 7 months, four aged 8 to 11 months, and five aged 12 to 17 months), or 30 µg of PRP and 326 µg of NOMP (six aged 2 to 4 months, four aged 5 to 7 months, six aged 8 to 11 months, and six aged 12 to 17 months). This age distribution among the recipients of three different dosages was similar. The ethnic distribution was representative of our outpatient population: white, 37 (32%); Hispanic, 48 (42%); black, 24 (21%); and other, six (5%).

Clinical Observations

No serious reactions were noted, with the majority being limited to local complaints of pain, swelling, or redness at the injection site (24/115 [21%]) or appearing tired or irritable (24/115 [21%]). Fever (temperature >38.0°C) was noted in eight (7%) of the recipients. There was no apparent increase in reactions following the second vaccine dose.

Serologic Response

Anti-PRP antibody GMTs increased from 0.09 to 3.28 mg/L and 6.61 mg/L following each dose of PRP-NOMP, respectively, in the 2- to 18-month age group. In the older age group, the anti-PRP antibody GMTs increased from 0.12 to 5.88 mg/L following a single injection. Sixty-one

(92%) and 58 (95%; two children failed to return for the second vaccine dose) of the 2- to 18-month-old children had postimmunization anti-PRP antibody levels greater than 1.0 mg/L following the first and second doses of the PRP-NOMP, respectively. Forty-eight (98%) in the 19- to 42-month age group had anti-PRP antibody levels greater than 1.0 mg/L 1 month following vaccination. These antibody responses between children 2 to 18 months old and 19 to 42 months old did not differ significantly.

The preimmunization and postimmunization anti-PRP antibody levels did not differ significantly when evaluated by ethnicity, preexisting anti-PRP antibody levels, or gender. A statistically significant difference was noted when anti-PRP antibody levels were compared regarding dosage of the vaccine administered in the 2- to 18-month age group. After the second dose of vaccine, anti-PRP antibody GMTs ranged from 3.5 to 12.0 mg/L, which were statistically significantly different ($P=.021$, Table 1). In addition, when we compared antibody responses of the different vaccine dosages by subtracting the prevaccination anti-PRP antibody levels from antibody levels following the second dose of vaccine, the difference was again significant ($P=.046$).

Furthermore, we noted that although the differences in anti-PRP antibody levels between those receiving 7.5 µg of PRP and 82 µg of NOMP and 15 µg of PRP and 163 µg of NOMP or 15 µg of PRP and 163 µg of NOMP and 30 µg of PRP and 326 µg of NOMP were not significant, the difference between the 7.5 µg of PRP and 82 µg of NOMP group vs the 30 µg of PRP and 326 µg of NOMP group was significant ($P=.05$). These differences could not be explained by the differences in the ages of each group or the differences in time interval between administration of vaccine and phlebotomy. However, anti-PRP antibody levels in the 19- to 42-month age group did not differ significantly when analyzed by the dosage of vaccine administered (Table 2).

COMMENT

The PRP-NOMP vaccine was well tolerated and found to be highly immunogenic in children 2 to 42 months of age, with 92% of children 2 to 18 months of age and 98% of the 19- to 42-month age group achieving what may be a so-called protective postimmunization antibody level (ie, ≥ 1.0 mg/L¹⁴) following a single dose of PRP-NOMP.

The intriguing finding was that the immunogenicity of PRP-NOMP in 2- to 18-month-old children appeared to be inversely related to the amount of PRP administered. This was shown by our demonstration that significantly greater anti-PRP antibody levels were achieved following the second dose in the recipients of PRP-NOMP containing 7.5 μ g of PRP compared with those receiving 30 μ g of PRP. The reasons for this inverse relationship between immunogenicity and vaccine dosage are unclear. Tudor-Williams et al,¹⁵ utilizing *H influenzae* type b oligosaccharide-protein conjugate vaccine (at 3, 5, and 9 months of age), have reported rises in anti-PRP antibody GMTs from 0.11 mg/L at 3 months to 14.6 mg/L at 10 months in recipients of a 2- μ g vaccine dosage vs 0.11 to 26.4 mg/L in recipients of a 10- μ g vaccine dosage. These findings suggest that immunologic responsiveness to *H influenzae* type b protein conjugate vaccines may differ. It should, however, be noted that the ethnic distribution of patients recruited by Tudor-Williams et al in Oxford, England, is different from our population base and that 0.9% sodium chloride was used as a diluent instead of our aluminum hydroxide-containing diluent.

Potential explanations for our findings might relate to components of PRP-NOMP, ie, PRP, carrier protein (group b meningococcal outer membrane protein) or aluminum hydroxide-containing diluent, but no data are available at present to support or refute any of these hypotheses. Taylor and Baker¹⁶ have demonstrated suppression of antibody response to type III pneumococcal antigen in mice when prior priming with antigen had been performed. These investigators have suggested that a soluble suppressor factor might be released from suppressor T cells after antigenic stimulation, which may later inhibit antigen-stimulating B cells or inhibit amplifier T cells when reexposed to the polysaccharide antigen. We were not able to demonstrate a soluble factor responsible for our dose-dependent phenomenon, and this hypothesis remains speculative.

Another potential explanation might be a so-called carrier-induced epitope suppression. Di John et al¹⁷ have shown, in studies of malaria vaccines coupled with a tetanus carrier, that prior immunity against a carrier protein modulates the serologic response to injected malaria peptides attached to the same carrier in humans. A statistically significant negative correlation was observed between preimmunization tetanus antitoxin titers and postimmunization response to a malaria sporozoite antigen. In our study, 2- to 18-month-old children responded to the first injection of 30 μ g of PRP, with postimmunization anti-PRP antibody levels being similar to those achieved with 7.5 or 15 μ g of PRP, but did not show greater booster responses with subsequent injection. It remains to be determined whether this lack of booster response stems from epitope suppression due to prior exposure to the carrier protein or whether there may have been antigenic competition. A complicating factor to exploring this concept was that stan-

dardized assays were not available to measure antibody to the outer membrane protein carrier.

Mannhalter et al¹⁸ have demonstrated in vitro that aluminum hydroxide, when utilized as an adjuvant with tetanus toxoid, may increase the interleukin 1 release from monocytes, resulting in increased antibody production by B cells. However, these investigators also demonstrated a decrease in cellular proliferation when booster antigen rechallenge contains aluminum hydroxide adjuvant. Similarly, Stewart-Tull,¹⁹ in a rabbit model utilizing influenza vaccine, has noted that repetitive injections of an adjuvant substance reduce the titer of anti-influenza antibody. However, this possibility appears to be very unlikely, because aluminum hydroxide contained in each 0.5-mL vaccine would be identical (0.225 mg), regardless of dosages.

The differences in immunogenicity observed in our study after two doses of PRP-NOMP containing 7.5, 15, or 30 μ g of PRP may not be clinically important, as almost all the children achieved anti-PRP antibody levels greater than 1.0 mg/L. However, further investigations of factors that may affect immune responsiveness to polysaccharide-protein conjugate vaccines are warranted to establish optimal vaccine dosage in young children.

This work was supported in part by a research grant from Merck Sharp & Dohme Research Laboratories, West Point, Pa.

We thank Dr Philip Vella of Merck Sharp & Dohme Research Laboratories for quantitation of anti-PRP antibody and Caroline Rivera and Lillian Vivona for typing the manuscript.

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Apparent Decreased Risk of Invasive Bacterial Disease After Heterologous Childhood Immunization

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Bruce Fireman, MS; Peter Christenson, PhD; Dominique Lampert, MS

● To investigate the possibility that there might be an increased risk of heterologous invasive bacterial disease after routine childhood immunization with measles, mumps, and rubella vaccine live; diphtheria and tetanus toxoids and pertussis vaccine; and oral poliovirus vaccine live, a case-control study was conducted within the Kaiser Permanente Northern California pediatric population. Contrary to the premise, an apparent protective effect against invasive bacterial disease was detected after all childhood vaccinations. However, when adjustment was made for frequency of well-care visits and day-care attendance, no significant relationship was seen between receipt of routine childhood immunizations and risk of invasive heterologous bacterial disease for any individual vaccine, although a statistically significant protective effect was detected within 1 or 3 months after the receipt of any vaccine. Since a decreased risk of invasive bacterial disease was also noted to be related to the receipt of routine well-child pediatric care, other preventive health care measures may be responsible for the apparent immunization protective effect.

(AJDC. 1991;145:746-749)

Shortly after release of the polyribosyl phosphate *Haemophilus influenzae* type b vaccine, a possible increased risk of acquiring invasive disease due to *H influenzae* during the 3-week period after receipt of the polyribosyl phosphate vaccine was reported.¹ More recently, in a field trial of two acellular pertussis vaccines in Sweden, it was observed that four vaccinees, but no controls, died of inva-

munizations, a study was undertaken to investigate the relationship, if any, between risk of heterologous bacterial disease and receipt of diphtheria and tetanus toxoids and pertussis (DTP) vaccine; measles, mumps, and rubella (MMR) virus vaccine, and oral poliovirus (OPV) vaccine live immunizations during the first 2 years of life.

PATIENTS AND METHODS

Invasive bacterial disease occurring in children between ages 1 month and 2 years in the Kaiser Permanente Medical Care Program of Northern California during the years 1986 through 1988 were identified from a computerized microbiology laboratory database. The medical records of all cases were reviewed to verify that each child had invasive bacterial disease as defined by a positive bacterial culture from a normally sterile site. Two controls were selected from the Kaiser Permanente Medical Care Program membership and matched to individual cases with respect to age (± 1 month), sex, zip code of residence, and duration of health plan membership. A chart review was conducted of all cases and controls to record all immunizations within 3 months of the index date, defined as the date of onset of invasive bacterial disease for the cases and the corresponding reference date for the matched controls. The reference date for controls was the date of diagnosis for the corresponding patient. In addition, telephone interviews were conducted with the parents of cases and controls to obtain information on possible covariates, including day-care, breastfeeding, parental ethnicity, parental education, and crowding. Subsequent to the initial analysis, an additional chart review was conducted to investigate frequency of well-care visits as a possible covariate. In this review, the total number of well-care visits that had occurred for each child within 6 months before the onset of illness for cases and the corresponding reference date for controls was obtained. Possible predictors of disease include immunization within specific intervals prior to the index date and the potential covariates. Individual conditional logistic regression models that recognize case-control matching were used to assess the effect of possible predictors individually on disease. Multiple conditional logistic regression was then used to determine the adjusted effect of recent immunization on disease by controlling for significant confounding covariates. Odds ratios relating immunization and disease were calculated from the regressions.⁴

RESULTS

Between January 1986 and December 1988, 223 cases of invasive bacterial disease were identified by the Kaiser Permanente Medical Care Program Regional Microbiology Laboratory. Of these, 144 were due to *Pneumococcus*, 58 due to *H influenzae*, seven due to *Escherichia coli*, five due

See also pp 734 and 750.

sive bacterial disease during the follow-up period.^{2,3} Because of these reports regarding the possibility of an increased risk of bacterial disease following childhood im-

Accepted for publication December 21, 1990.

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Table 1.—Cases and Controls Immunized at Specified Intervals Prior to Onset of Disease*

Interval, d	Vaccine	% Immunized		Odds Ratio†		
		Cases (n = 223)	Controls (n = 438)	Estimate	95% CI	P
0-7	DTP	1.4	3.0	0.44	(0.12-1.60)	.21
	OPV	0.9	2.6	0.34	(0.07-1.59)	.17
	MMR	0	0.9	
	Any‡	1.4	4.0	0.34	(0.10-1.18)	.09
8-30	DTP	1.9	10.0	0.17	(0.06-0.47)	.001
	OPV	0.9	8.6	0.10	(0.02-0.41)	.001
	MMR	0.5	0.9	0.50	(0.06-4.47)	.53
	Any‡	2.3	11.2	0.19	(0.07-0.49)	.001
31-60	DTP	4.2	10.0	0.36	(0.16-0.78)	.01
	OPV	3.7	7.7	0.44	(0.19-1.00)	.05
	MMR	0.5	1.6	0.25	(0.03-2.19)	.21
	Any‡	4.7	11.9	0.34	(0.16-0.70)	.003
61-90	DTP	0.5	6.1	0.07	(0.01-0.51)	.01
	OPV	0	6.8
	MMR	0	2.3
	Any‡	0.5	7.9	0.05	(0.01-0.40)	.004

*DTP indicates diphtheria and tetanus toxoids and pertussis vaccine; OPV, oral polio virus vaccine live; MMR, measles, mumps, and rubella vaccine live; and CI, confidence interval.

†Ratio of the odds of disease among children vaccinated in the interval to the odds of disease among children not vaccinated in the interval, obtained from conditional logistic regression.

‡DTP, OPV, or MMR.

to *Meningococcus*, and nine due to other organisms. The age range of cases was between 1 and 20 months with most disease occurring between 5 and 15 months of age. Chart review was accomplished for 221 of 223 cases and 438 of 446 controls. Telephone interviews were completed for 202 of 223 cases and 414 of 446 controls.

The percentage of cases and controls immunized at specific intervals up to 3 months prior to onset of illness in the cases is shown in Table 1. Generally, controls were about four times more likely to have been immunized within either 1 or 3 months than were cases. Odds ratios utilizing case-control matching translate immunization rates into ratios of likelihood of disease. (An odds ratio of 1 would indicate no difference between cases and controls.) Ignoring other factors related to disease, recent DTP or OPV immunization reduces the risk of disease by a factor of 0.07 to 0.44. Table 2 shows the potential for confounding the observed results. Thirty-one percent of cases attended day-care compared with only 16% of controls ($P < .0001$). Children in day-care were at significantly greater risk of disease than those who were not (odds ratio, 2.40). In contrast, cases had significantly fewer well-care visits than controls ($P < .0001$). They had an average of 1.1 well-care visits within 6 months prior to onset of illness, whereas controls had an average of 2.6 visits during the same period. Children with fewer well-care visits were at significantly greater risk of invasive bacterial disease (odds ratio, 4.0 for none to one visit vs two visits).

Table 3 shows adjusted odds ratios for day-care and frequency of well-care visits for 484 subjects for whom this information was available. (The other 177 subjects did not

Table 2.—Comparability of Cases and Controls in Potential Confounders of the Apparent Effect of Immunization on Disease

Potential Factor	Cases, %	Controls, %	P*
Maternal ethnicity†			
White	59	57	NS
Black	21	13	
Hispanic	12	14	
Asian	8	16	
Maternal education†			
High school	62	56	NS
College	25	28	
Professional	13	16	
No. of siblings			
None	34	36	NS
1	41	39	
2	16	17	
3 or more	8	8	
Breast-feeding	65	71	NS
Day-care attendance	31	16	<.0001
Well-child visits within 6 mo			
0 or 1	73	15	<.0001
2	23	22	

*Potential confounding factors were compared between patients and their matched controls in individual conditional logistic regressions that modeled the likelihood of disease depending on the status of the factor. NS indicates not significant.

†Ethnicity and education distributions for fathers are nearly identical to those for mothers.

Table 3.—Odds of Disease Based on Recent Immunization History, Adjusted for Day-Care Status and No. of Well-Care Visits Within 6 Months*

Interval, d	Vaccine	Receipt of Vaccine in Interval					OR†	
		Cases, %	Controls, %	OR†	95% CI	P	Day-Care	Well Care
0-7	DTP	0.6	3.8	0.38	(0.04, 3.53)	.40	1.94	0.10
	OPV	0.6	3.2	0.44	(0.05, 4.25)	.48	1.92	0.10
	MMR	0	1.0	1.92	0.10
	Any	0.6	4.7	0.27	(0.03, 2.33)	.23	1.95	0.10
8-30	DTP	1.8	7.6	0.37	(0.10, 1.41)	.15	1.95	0.10
	OPV	0.6	3.2	0.13	(0.02, 1.11)	.06	1.84	0.10
	MMR	0.6	1.0	0.16	(0.01, 2.33)	.18	1.90	0.09
	Any	2.4	10.1	0.29	(0.09, 0.95)	.04	1.94	0.10
31-60	DTP	4.8	10.4	1.02	(0.38, 2.76)	.96	1.92	0.10
	OPV	4.2	7.3	1.41	(0.50, 3.96)	.52	1.92	0.09
	MMR	0.6	1.9	0.70	(0.06, 8.76)	.78	1.92	0.10
	Any	5.4	12.3	0.97	(0.38, 2.45)	.95	1.92	0.10
61-90	DTP	0.6	5.1	0.31	(0.04, 2.50)	.27	1.85	0.10
	OPV	0	5.7	1.83	0.11
	MMR	0	2.5	1.88	0.10
	Any	0.6	6.9	0.21	(0.03, 1.63)	0.14	1.81	0.10

*OR indicates odds ratio; CI, confidence interval; DTP, diphtheria and tetanus toxoids and pertussis vaccine; OPV, oral polio virus vaccine live; and MMR, measles, mumps, and rubella vaccine live. Day-care status, well-child care visits, and vaccine history were available for 167 patients and 317 controls.

†Ratio of the odds of disease among children vaccinated in the interval to the odds of disease among children not vaccinated in the interval, obtained from conditional logistic regression models, which adjust for day-care status and number of well-child care visits within 6 months. Odds ratios for day care (yes vs no) and well-child care (at least two visits vs at most one) are similarly adjusted for each other and for vaccination in the interval.

differ in vaccination rates from these 484 subjects.) There was still a tendency for recently immunized children to have less risk of disease, but for most vaccines and intervals the odds ratios shifted toward the no-effect value of 1.0. The apparent contradictory odds ratio of 1.41 for OPV 31 to 60 days prior to the reference date was due to proportionally more cases than controls with none or one well-care visit, and no OPV immunizations in this interval among these subjects. Among subjects with at least two well-care visits, 14% of cases and 9% of controls received OPV in this interval. A similar phenomenon occurred for DTP in this interval.

During the 0- to 30-day interval for any vaccine, 3% of cases and 15% of controls were immunized. The odds ratio was 0.26 (95% confidence interval [CI], 0.09 to 0.76; $P = .01$). Similarly, for the whole 90-day period for any vaccine, 9% of cases and 34% of controls were immunized (odds ratio, 0.31; 95% CI, 0.13 to 0.73; $P = .01$).

Day-care attendees are almost twice as likely to develop disease, and children with at least two well-care visits in 6 months are at one tenth the risk of disease as are children with at most one well-care visit.

COMMENT

We have investigated a possible increased risk of heterologous invasive bacterial disease following routine immunizations in early childhood. In this case-control study we observed an apparent protective effect of MMR, DTP, or OPV against the development of invasive bacterial disease for a 1- or 3-month period. When the data were an-

alyzed for available information on covariates including socioeconomic indicators, race, and day-care attendance, only day-care was found to be a potential confounder. However, this possible confounding was in the direction of increasing the apparent protective effect of vaccination; children in day-care are both at increased risk of bacterial disease and more likely to be vaccinated. Subsequently, a second chart review was undertaken to determine the frequency of well-care visits among cases and controls. In this second review, it was found that children who received well care were significantly less likely to develop invasive bacterial disease than those who had few or no well-care visits. With adjustment for this confounder, the apparent protective effect of routine childhood immunization against subsequent heterologous invasive bacterial disease was greatly diminished in magnitude and precision, and became a statistically nonsignificant trend for each vaccine considered individually.

It is possible that the apparent difference in disease risk between cases and controls is the result of selection bias. That is, children who were ill at the time of their well-care visits were less likely to be immunized than children who were well. However, if this were the explanation for the observed difference, one would have expected that cases would have been less likely to be immunized, but not less likely to receive well care. If deferral of immunization in sick children accounted for the observed results, one would have expected the number of well-care visits to be the same.

The biologic plausibility of a protective effect of routine childhood immunization with DTP, OPV, and MMR must

be considered. Endotoxin, a component of the pertussis portion of the DTP vaccine, is a known protective factor against experimental bacterial infections.⁵ In one experiment, protection induced by *Bordetella pertussis* was still present 49 days after vaccine administration. Infection with the measles virus elicits the production of interferon, and this may offer protection against other viral infections.⁶ Since invasive bacterial disease may have a relationship to respiratory viral infections it is possible that MMR immunization could also be a factor in decreasing the occurrence of invasive bacterial disease.⁷ However, since the protective findings in this study were uniform over a 3-month period, it is difficult to attribute them solely to the vaccine properties discussed above.

Based on our data, we conclude that there is no evidence of an increased risk of invasive bacterial disease following any of the routine childhood immunizations investigated; on the contrary, there is a trend toward lower rates of disease among children after receiving these immunizations. Furthermore, the receipt of routine well-child pediatric care is associated with a decreased risk of invasive bacterial disease that appears to be unrelated to the receipt of childhood vaccinations and may relate to other factors such as nutrition counseling, other preventive health care measures, or an increased level of health consciousness and hygiene among parents bringing their children in for well-care visits.

Although a protective effect of the vaccines is biologically plausible, it is possible that the apparent protective

effect is related to good health practices that are only partially reflected in well-child care visits.

This study was funded by an unrestricted grant from Lederle Laboratories, Pearl River, NJ, and by the Community Services Program of the Northern California Permanente Medical Group.

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DTP Immunization and Susceptibility to Infectious Diseases

Is There a Relationship?

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● A two-part study was carried out in Alaskan Native children to evaluate the potential risk of invasive bacterial disease and the occurrence of minor illnesses after immunization with diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP). First, a case-control comparison was performed with 186 children who had invasive *Haemophilus influenzae* type b or *Streptococcus pneumoniae* disease (cases) and 186 healthy controls matched for sex, region of residence, birth date, and number of DTP immunizations. The proportion of cases and controls immunized in the 30-day period before onset of disease for cases or reference date for controls was identical, suggesting no association with DTP immunization. In a second analysis, the occurrence of any illness, particularly infectious diseases, in 104 study subjects was compared for the period 30 days before and after 377 DTP immunizations. The rate of illness before immunization was 53%, and after immunization, 43%, again suggesting no causative effects from DTP immunization. Despite the high rates of invasive bacterial disease and nearly complete DTP immunization status in this population, no consistent relationship could be demonstrated between DTP immunization and susceptibility to infectious diseases.

(AJDC. 1991;145:750-754)

Until recently, little attention has been given to the possibility that pertussis vaccination might affect the

conducted in Sweden in 1986 and 1987, it was observed that three pertussis vaccinees died of invasive bacterial infections.^{1,2} In another recent study, infants who were immunized with diphtheria and tetanus toxoids and whole-cell pertussis vaccine (DTP) subsequently had an increased rate of fever, cough, and diarrheal illness.³

To examine these issues further, we evaluated in Alaska Native infants the potential risk of, or protection from, invasive bacterial disease and other minor illnesses after DTP immunization. We selected the Alaskan Native American population (Eskimo, Indian, and Aleut) for this study because they suffer the highest known incidence of invasive *Haemophilus influenzae* type b and *Streptococcus pneumoniae* disease, and detailed surveillance data for these diseases are available for the past 10 years.^{4,5} Also, there is a concerted statewide effort to immunize all Alaskan children with DTP, and the state maintains computerized immunization records. In this study we performed two analyses: (1) to evaluate the temporal relationship of DTP immunization in children with and without invasive *H influenzae* type b and *S pneumoniae* disease and (2) to evaluate in those children with complete medical record reviews the occurrence of any illness, particularly infectious diseases, in the 30-day period before and after DTP immunization.

SUBJECTS AND METHODS

Study subjects were Alaskan Native American Eskimos, Indians, or Aleuts residing in two health service areas of the Alaska Area Indian Health Service: the Yukon-Kuskokwim Delta and the Anchorage service units.

Case-Control Analysis

Cases had invasive *H influenzae* type b or *S pneumoniae* disease proved by culture of specimens obtained from normally sterile body sites (blood, cerebrospinal fluid, empyema, or joint space) during the period from January 1, 1980, through April 1988 and were 2 to 24 months old with at least one previous DTP immunization. Cases were detected by both active and passive surveillance for invasive *H influenzae* type b and *S pneumoniae* diseases, as previously described.^{4,5} Children who had received previous *H influenzae* type b vaccines were excluded.

For each case, one control was selected from computerized birth logs starting from the birth date of the case and matching for birth date, sex, residence within the same service unit, and the number of DTP immunizations given at the time of disease

See also pp 734 and 746.

susceptibility of children to other infectious diseases. However, in a large acellular pertussis vaccine efficacy trial

Accepted for publication December 25, 1990.

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Table 1.—Characteristics and Comparability of Cases and Controls*

	No. (%)	
	Cases	Controls
Matched Characteristics		
Gender		
M	103 (55)	103 (55)
F	83 (45)	83 (45)
Region		
Anchorage Service Unit	42 (23)	42 (23)
Yukon-Kuskokwim	144 (77)	144 (77)
No. of DTP immunizations before disease diagnosis or reference date		
1	48 (26)	48 (26)
2	39 (21)	39 (21)
3	89 (48)	89 (48)
4	10 (5)	10 (5)
Age at disease diagnoses or reference date		
Mean \pm SD, mo	10.5 \pm 5.0	10.5 \pm 5.0
Under 1 y	118 (63)	118 (63)
Unmatched Characteristics		
Ethnicity (Native American)		
Eskimo	159 (85)	162 (87)
Indian	12 (6)	10 (5)
Aleut	13 (7)	13 (7)
Mixed Eskimo/Indian	2 (1)	1 (1)
Proportion Alaskan native		
<4/8	14 (10)	21 (13)
4/8	24 (17)	28 (17)
5/8-7/8	10 (7)	5 (3)
8/8	96 (67)	106 (66)
Unknown	42	26
Maternal parity at birth of study subject		
1 (1st child)	55 (30)	50 (28)
2	43 (24)	49 (27)
3	33 (18)	25 (14)
4	24 (13)	25 (14)
5	17 (9)	17 (9)
>5	9 (5)	13 (7)
Unknown	5	7
Birth weight		
<2500 g	11 (6)	8 (4)
Mean \pm SD, g	3423 \pm 563	3525 \pm 546
Maternal age at birth of study subjects, y (mean \pm SD)	26.3 \pm 5.7†	27.5 \pm 5.5

*DTP indicates diphtheria and tetanus toxoids and whole-cell pertussis vaccine.

† $P = .04$ when compared with age of mothers of controls. All other comparisons not significantly different.

diagnosis. When cases were from small communities (under 1000 population), controls were selected from a distant village within the same service unit. This was done to avoid overmatching, resulting from coincident immunizations in a village administered by a visiting public health nurse. Controls were excluded if they had a history of pneumonia, meningitis, cellulitis, sepsis, or arthritis diagnosed during the first 24 months of life or if they had received any *H influenzae* type b vaccines. To compare intervals from immunization, a reference date for the controls was established. This reference date was the day that the control was the same age as his or her matched case at the time of diagnosis of *H influenzae* type b or *S pneumoniae* disease.

All available medical records for both cases and controls, including the public health nurse immunization records, were reviewed to verify and identify all vaccinations, illnesses, birth weight, maternal age, and birth order. Computerized Indian Health Service medical record summaries were also searched for illness and immunization data. Cases and controls were com-

pared with respect to the interval from the last DTP immunization to the diagnosis date of illness for cases or to the reference date for controls.

Statistical analyses included McNemar's test to compare the proportion of cases and controls having recent immunizations and the paired *t* test to compare mean interval differences. A conditional logistic regression analysis of case-control differences for maternal age, parity, birth weight, ethnicity, and interval since last immunization was also used to detect effects of potential confounders.⁶ Odds ratios and their confidence limits were calculated for varying intervals between immunization and the date of diagnosis of invasive bacterial disease for cases or reference date for controls.⁷

Analysis of All Illnesses

The complete medical records for both outpatient and inpatient encounters were available for 104 cases and controls who resided in the communities of Bethel and Anchorage. These records were reviewed for the occurrence of all illnesses, including minor infectious diseases, during the periods 30 days before and after each DTP immunization. For all illness and selected infectious illness, McNemar's test was used to compare the occurrence of illness in the prevaccine vs postvaccine periods for cases and controls and for the two combined.

RESULTS

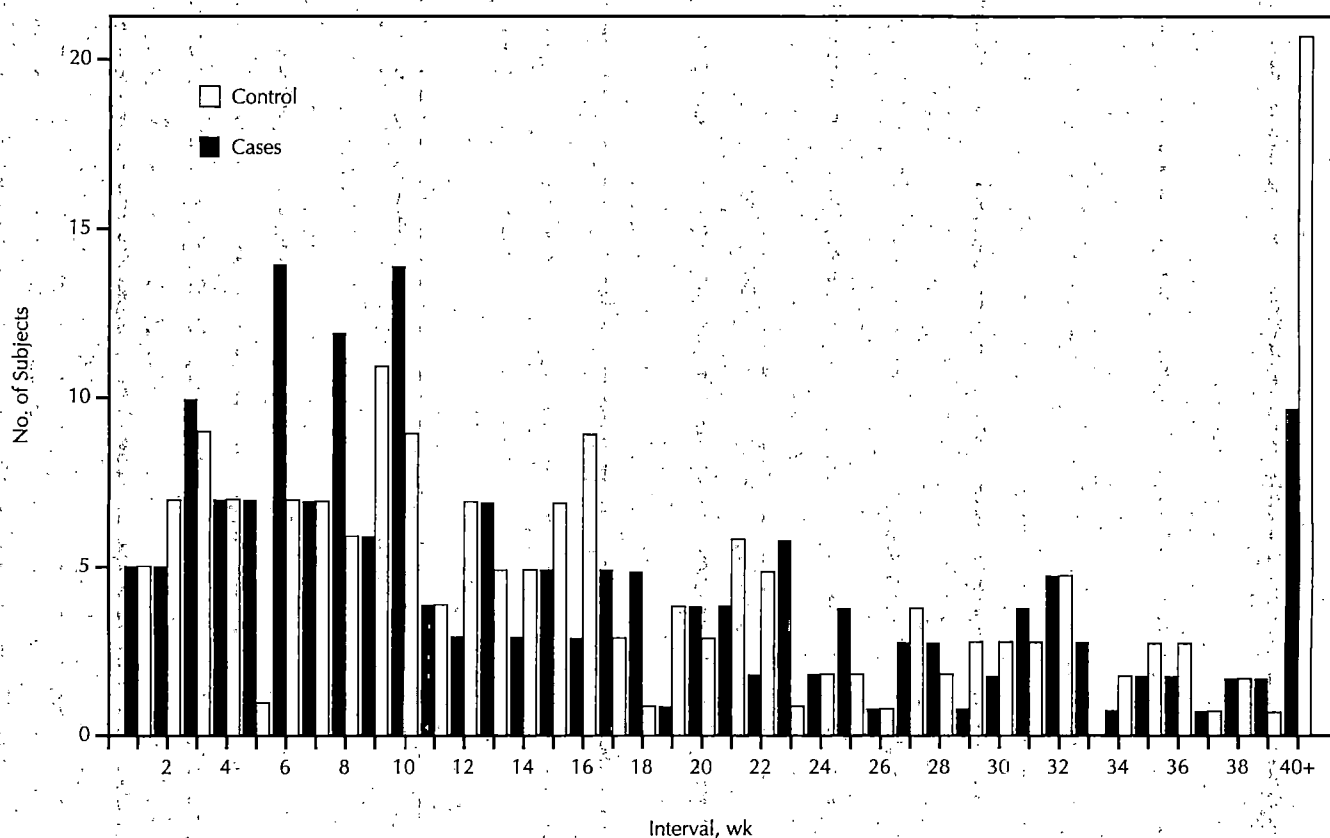
Cases

During the study period, there were 179 *H influenzae* type b and 94 *S pneumoniae* cases of invasive disease in Alaskan Native children between 2 and 24 months of age at the time of diagnosis. Of this group, 55 cases of invasive *H influenzae* type b and 32 cases of *S pneumoniae* disease were excluded from the study for one of three reasons: (1) they had participated in an *H influenzae* type b conjugate vaccine trial ($N = 37$); (2) they lacked previous DTP immunization or could not be adequately matched to a control child ($N = 30$); or (3) they had not yet been reported on by surveillance at the time of study ($N = 20$). There were five cases with more than one episode of invasive bacterial disease; only the first illness was considered. In the final analysis, there were 124 *H influenzae* type b and 62 *S pneumoniae* cases with matched controls. Of these cases, 31.2% had meningitis, 27.4% had pneumonia, 0.6% had epiglottitis, 12.4% had arthritis, 10.1% had cellulitis, and 18.4% had septicemia/bacteremia.

Case-Control Analysis

The characteristics and comparability of cases and controls are shown in Table 1. The mean age of the mothers of cases was 26.3 years, whereas it was 27.5 years for mothers of controls ($P = .04$). There were no other significant differences between the groups. The birth dates of 69% of the case-control pairs were 14 days or less apart; only 3% were more than 60 days apart.

Shown in the Figure are the weekly intervals from last DTP immunization to date of disease diagnosis for cases or from last immunization to the reference date for controls. Considerable weekly variations occurred for both cases and controls. However, in the 1st month after immunization, the distribution of individuals in weekly intervals after DTP immunization was equal for cases and controls. Cases predominated intermittently over controls for the 5th through the 10th weeks after immunization. Controls predominated over cases or were equal to cases for 19 of the 30 subsequent intervals analyzed.



Time from the most recent immunization to the diagnosis of invasive *Haemophilus influenzae* type b or *Streptococcus pneumoniae* disease for cases or the matched reference date for healthy controls.

Analyses stratified for first, second, third, or fourth recommended DTP immunizations at approximately 2, 4, 6, and 18 months of age were also performed, and no associations were found. Therefore, only the combined data are presented.

In the categoric analysis in Table 2, the numbers of cases and controls are presented by specified intervals from the last DTP immunization to the date of disease diagnosis or reference date. The numbers of cases and controls who were immunized within 30 days of disease onset or reference date respectively were identical. Of the seven periods examined, the combined odds ratio was 1 for the first three, slightly greater than 1 for the next two, and below 1 for the final two. The only variation of note was in the 31- to 60-day period for invasive *S pneumoniae* disease. Immunization occurred in 19 cases and only 10 controls ($P = .05$; odds ratio, 3.3, with a confidence interval of 1.1 to 10). A similar trend for *S pneumoniae* disease was noted in the 61- to 90-day period.

The mean interval from the last DTP to diagnosis was 110 days for cases compared with 128 days to the reference date for controls; the corresponding medians were 80 and 101 days, respectively ($P < .05$). A similar analysis was repeated separately for meningitis, and no significant case-control differences were found, nor was there an imbalance in the 31- to 90-day interval. A multivariate logistic regression analysis of the variables shown in Table 1 and the intervals in Table 2 also revealed no additional associations between DTP vaccination and disease.

Analysis of All Illnesses

To evaluate further any possible temporal association between illness and DTP immunization, the occurrence of any illness during the 30-day period before and after DTP

administration was compared for the subset of infants for whom all medical records were available (Table 3). For this analysis, there were only minor differences between cases and controls, and therefore the two were combined for the analysis in Table 3. For all categories examined, a higher proportion of the 30-day patient intervals before (rather than after) immunization had any illness. This was also true for all of the infectious disease illnesses. These differences achieved statistical significance only for all illnesses combined (53% vs 43%; $P < .004$) and likely reflects the fact that immunizations are usually withheld from ill children (well-child effect; see the "Comment" section). During the first 18 months of life, total minor infectious illnesses were more common in infants who developed invasive bacterial disease (0.98 episodes per month) than in infants without invasive bacterial disease (0.67 episodes per month).

COMMENT

In animal-model systems, pertussis vaccine and isolated pertussis antigens have been found to have an effect on the susceptibility of the animals to other bacteria and to viruses; in some systems protection is observed, and in others increased susceptibility occurs.⁸⁻¹⁷ In most of these systems, the effects are short-lived; the bacterial or viral challenge must occur within a few days of immunization. The most persistent effect was noted in a mouse adenoviral system in which pertussis vaccine rendered the mice resistant to the virus for a period of 5 to 35 days after immunization.¹⁵

In a traditional case-control study, patients with a particular disease (ie, cases) are compared with randomly selected or matched controls without disease to assess the relative prevalence of some associated risk factor. One

Table 2.—Number of Hib and Sp Cases and Controls With DTP Immunization During Specified Time Intervals Before Onset of Disease in Cases and Reference Date in Controls*

Interval, d	Category	No.		Pt	Odds Ratio† (95% Confidence Interval)
		Cases	Controls		
≤3	Hib	2	2	1.0	1.0 (0.05-20.9)
	Sp	0	0
	Total	2	2	1.0	1.0 (0.05-20.9)
4-7	Hib	2	1	.6	2.0 (0.2-22.1)
	Sp	1	2	.6	0.5 (0.0-15.3)
	Total	3	3	1.0	1.0 (0.2-5.0)
8-30	Hib	19	17	.8	1.2 (0.5-2.8)
	Sp	4	6	.8	0.7 (0.2-2.4)
	Total	23	23	1.0	1.0 (0.5-2.0)
31-60	Hib	21	21	1.0	1.0 (0.5-2.0)
	Sp	19	10	.5	3.3 (1.1-10.0)
	Total	40	31	.3	1.4 (0.8-2.5)
61-90	Hib	23	21	.9	1.2 (0.6-2.4)
	Sp	9	3	.08	7.0 (0.9-57.0)
	Total	32	24	.3	1.6 (0.8-3.1)
91-120	Hib	13	18	.5	0.7 (0.3-1.5)
	Sp	4	8	.3	0.3 (0.07-1.7)
	Total	17	26	.2	0.6 (0.3-1.2)
>120	Hib	44	44	1.0	1.0 (0.5-2.2)
	Sp	25	33	.06	0.3 (0.08-1.0)
	Total	69	77	.3	0.7 (0.3-1.3)

*Hib indicates *Haemophilus influenzae* type b; Sp, *Streptococcus pneumoniae*; and DTP, diphtheria and tetanus toxoids and whole-cell pertussis vaccine.

†McNemar's test, using case-control matching.

‡Ratio of the odds of a case being immunized in the specified interval relative to the odds of its controls being immunized in the same interval.

purpose of matching is to eliminate potential confounding effects. The present study is different from a classic case-control study, because the prevalence of DTP immunization is, by design, equivalent for cases and controls. What we evaluated was the temporal proximity of DTP immunization to the occurrence of invasive bacterial disease, concentrating on the earliest time intervals. Our hypothesis is that a cause-and-effect relationship would lead to shorter intervals for the cases relative to controls.

The possibility of overmatching should be considered as a possible explanation for the lack of differences in this study. By matching too closely, one might select a control group that is too much like the cases for all factors, including timing of DTP immunizations. In our study, considerable effort was made to eliminate confounding effects by carefully defining and restricting both the study cases and controls for potential confounding factors and matching the controls only for potential confounders (factors that might influence the timing of immunization or the risk of bacterial disease). Previous DTP immunization was such a matching/confounding factor. Nearly all Alaskan Natives are immunized, and minor infectious illnesses are more common for *H influenzae* type b and *S pneumoniae* cases than controls during the first 18 months of life, frequently resulting in postponement of immunization. Without matching on the number of immunizations, cases would have received fewer DTP doses, suggesting a pro-

Table 3.—Occurrence of Illnesses in 104 Study Subjects Within a 30-Day Interval Before and After 377 DTP Immunizations*

Illness Category	No. of Subject-Intervals (%) With Illness Before Immunization	No. of Subject-Intervals (%) With Illness After Immunization	P (McNemar's Test)
Any illness	198 (53)	162 (43)	.004
Any infectious disease	163 (43)	141 (37)	.084
Otitis media	78 (21)	70 (19)	.501
Other respiratory infections	77 (20)	65 (17)	.285
Temperature >38°C	50 (13)	46 (12)	.724
Hospitalization	11 (3)	7 (2)	.424

*DTP indicates diphtheria and tetanus toxoids and whole-cell pertussis vaccine.

TECTIVE effect. Also, matching on the number of DTP doses seemed reasonable to reduce potential confounding effects related to overall health status. Importantly, we did not match for village of residence, which would have overmatched the cases and controls. The lack of rigid immunization schedules in this remote population of Alaskan Natives likely provides sufficient variability in the timing of DTP immunization to permit evaluation of time intervals as an outcome measure.

In this investigation, we found no clear temporal relationship between DTP immunization and risk of invasive bacterial infection or the risk of common pediatric illnesses. This was particularly true for the 1-month interval after immunization. The finding that immunization occurred in 19 *S pneumoniae* cases and in only 10 controls during the 31- to 60-day period deserves comment. This may be a chance occurrence, since only one significant result was observed in Table 2. It seems unlikely that a biologic effect resulting from DTP vaccine would be seen only during the 2nd month and not the 1st month. Also, there is no reason for a relationship to occur for *S pneumoniae* but not *H influenzae* type b disease, especially when there were more than twice as many *H influenzae* type b cases to evaluate. Finally, there was no evidence or trend of an increase in common illnesses, particularly infectious disease illnesses, after DTP immunization in either healthy infants or those with invasive bacterial disease.

Our results do not support the concerns raised by the Swedish acellular pertussis study of increased risk of bacterial disease and case fatality.² However, our study only looked at disease occurrence and not mortality, as fatal cases of *H influenzae* type b and *S pneumoniae* disease in Alaska are too rare for analysis (3% to 4% case fatality in Alaskan Native infants).^{4,5}

In contrast to the findings in a small Israeli study by Jaber and associates,³ we found no increase in common illnesses, including infectious diseases, in the month after immunization.⁵ In fact, we noted more illnesses in the month before vaccination than in the subsequent month. This finding is likely influenced by the fact that immunizations are frequently deferred in children with infectious illnesses until they are well, thereby artificially increasing

the rate of illnesses before immunizations are given. This "well-child effect" is the likely explanation for our observations. Recently, Joffe and colleagues¹⁸ reported that children hospitalized with infectious illnesses in the Colorado Kaiser Foundation Health Plan had a rate of immunization in the preceding month that was equivalent to the rate in matched controls.

In conclusion, we found no consistent evidence that DTP immunization has a temporal association with the occurrence of invasive bacterial disease in children, and we found no evidence that the risk is increased for any illnesses, particularly infectious diseases, after immunization.

These studies were funded by an unrestricted grant from Lederle Laboratories, Pearl River, NY, and by contract N01-AI-32512 from the National Institute for Allergy and Infectious Disease, National Institutes of Health, Bethesda, Md.

The authors gratefully acknowledge the comments of Robert Chun, MD, and Robert Wainwright, MD, and the assistance of Alice Christian, RN, Annette Harpster, RN, Patty Schnitzer, RN, MSN, Debbie Parks, Alice Mueller, Joseph Mannion, Denise Tritt, Rose Eward, and Emily Klees.

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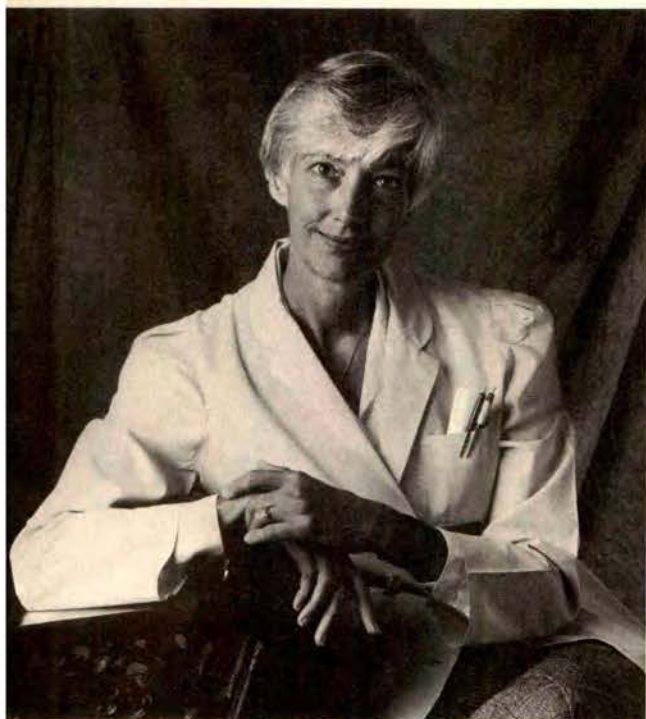
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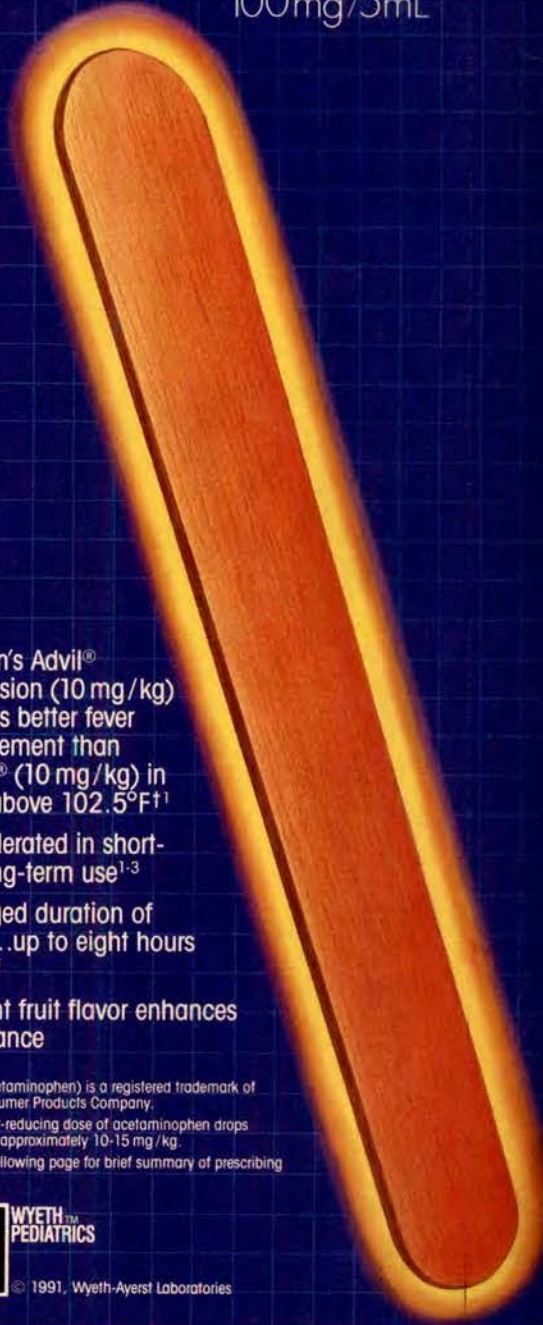
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CHILDREN'S ADVIL® SUSPENSION is also indicated for relief of the signs and symptoms of juvenile arthritis, rheumatoid arthritis, and osteoarthritis.

CHILDREN'S ADVIL® SUSPENSION is indicated for the relief of primary dysmenorrhea.

CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis: Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: Coumarin-type Anticoagulants: Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H₂ Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofenic effect of furosemide and thiazides in some patients.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain; fullness of the GI tract (bloating and flatulence); heartburn; indigestion, nausea; nausea and vomiting; dizziness; headache, nervousness, pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention; (generally responds promptly to drug discontinuation).

Possible Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis, alopecia, erythema, multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions; aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence; amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision); hearing loss; agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations, anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria; dry eyes and mouth, gingival ulcers, rhinitis.

Possible Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri; photoallergic skin reactions, toxic epidermal necrolysis; cataracts, conjunctivitis, diplopia, optic neuritis; bleeding episodes (e.g., epistaxis, menorrhagia); acidosis, gynecomastia, hypoglycemic reactions; arrhythmias (sinus tachycardia, sinus bradycardia); angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness, renal papillary necrosis.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles.

Caution: Federal law prohibits dispensing without prescription.

References:

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3. Independent Clinical Study: Reduction of Fever in Children, Single Dose. Data on file, Medical Department, Whitehall Laboratories.



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Objective Structured Clinical Examination in a Pediatric Residency Program

Bahman Joorabchi, MD, MEd

● This report describes and evaluates a 42-station objective structured clinical examination (OSCE) administered to 29 pediatric residents and six medical students. In half of the stations, residents spent 5 minutes performing a clearly defined clinical task while being rated by an observer. In the other half of the stations, they answered questions based on the data just gathered. There were six interviews with real or simulated patients, four physical examinations, six laboratory tests or procedures, and one chart review. Eight rest stops were provided. The results of the OSCE were compared with those of resident performance ratings and the Pediatric Board's in-training examination. The OSCE scores could clearly separate the students from the residents and each class of residents from all others (construct validity). The in-training examination could not separate first-year postgraduate level and second-year postgraduate level residents. Resident performance ratings could distinguish only first-year postgraduate level from third-year postgraduate level residents. Residents uniformly agreed that the OSCE measured important clinical objectives attesting to its content validity. Reliability for the OSCE was calculated at the 0.8 to 0.83 range. It is concluded that valid and reliable clinical examinations in pediatrics are feasible, practical, and highly desirable.

(AJDC. 1991;145:757-762)

Evaluation of clinical competence is a desired, but elusive, goal in medical education. Valid and reliable examinations are generally difficult, labor intensive, and costly. Furthermore, there is no deep-rooted tradition for clinical examination in this country. Despite pleas for reform,^{1,2} the prevalent certifying examinations (from National Boards to specialty boards) and the in-training examinations (ITE) rely on paper and pencil tests that measure only cognitive objectives of generally lower taxonomic levels. This is understandable given the difficulties of conducting any form of evaluation involving patients, simulated or real. Aside from the issue of costs, organization, and manpower, one has to grapple with inadequate samplings, subjective scoring, interrater variability,

and low reliabilities.

To overcome some of these problems, Harden and his associates³ introduced the objective structured clinical examination (OSCE), a multistation format that evaluates clinical skills and attitudes as well as cognitive objectives. In half the stations of this examination, the student carries out a clearly defined task such as a patient interview or physical examination or interpretation of test results, while an observer rates the performance. In the other half of the stations, the student answers open-ended or multiple-choice questions based on the clinical task just completed.

The method has been gaining in popularity and is widely used in Europe and in the Commonwealth countries.⁴⁻⁶ In the United States, only a few medical schools⁷⁻¹¹ and residency programs^{12,13} have used it. Mounting an OSCE in pediatrics is an especially difficult task. Only one small example involving two history stations, three physical examination stations, and seven laboratory stations given to medical students in three British medical schools has been reported.¹⁴⁻¹⁷ To my knowledge to date, there has been no report of an OSCE for pediatric residents.

This report details an experience in the use of OSCE to evaluate clinical competence in 29 pediatric residents and six medical students in a community-based residency

Department Editors.—Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—We teach, but how do we evaluate? This is one of our system's greatest problems. Joorabchi used a testing scenario, including simulated patients, real patients, and short case situations to assess resident and student learning. The tests were tested. See if this may be a useful approach for your program.—H.D.A.

Accepted for publication November 27, 1990.

From the Wayne/Oakland Child and Adolescent Medicine Program, Pontiac (Mich) General Hospital.

Reprint requests to Wayne/Oakland Child and Adolescent Medicine Program, Pontiac General Hospital, Pontiac, MI 48341 (Dr Joorabchi).

Table 1.—Contents of the OSCE*

The following is a list of professional skills, cognitive objectives, and affective objectives measured in each of the stations. The heading for each station includes the numbers and the name of the station, whether it was a laboratory, history, or physical examination station, and whether an observer was present.

Stations 1 and 2, Urinalysis.—Laboratory, no observer

Interprets a slide of an abnormal urinary sediment and the report of a urine culture

Recognizes a normal IVP

Decides on the need for further tests

Orders appropriate antibiotics

Stations 3 and 4, Bowlegs.—Laboratory, no observer

Detects the abnormalities in bone roentgenograms of a patient with rickets

Correctly interprets results of urine and blood tests

Arrives at a differential diagnosis

Stations 5 and 6, Cesarean Section.—History, observer present

Obtains an adequate history from the lying-in nurse (per observer checklist) while an emergency cesarean section is in progress

Arrives at a differential diagnosis on viewing four pictures of the newborn

Answers questions on characteristics of and differences between tremors, drug withdrawal, and neonatal seizures

Interprets the nurse's "activity chart" and growth grid recorded on the newborn

Writes appropriate hospital admission orders for the infant

Stations 7 and 8, Hearing.—Physical examination, observer present

Performs otoscopy and pneumotoscopy appropriately

Detects presence or absence of abnormalities of tympanic membrane appearance and motion

Detects conduction hearing loss in one ear grossly and by using a tuning fork

Lists at least six risk factors predisposing to hearing loss in a child

Stations 9 and 10, Rest Stations

Stations 11 and 12, Cholesterol.—History, observer present

Takes an appropriate history from a mother with a xanthoma diagnosed as hypercholesterolemia

Given the results of the lipid screening tests on the children arrives at the diagnosis of familial hypercholesterolemia

Uses appropriate interviewing skills (per observer checklist)

Discusses prognosis and gives nutritional advice to the family

Answers questions on the mode of inheritance (based on the family history) and on the mechanism of hypercholesterolemia

Stations 13 and 14, Swollen Ankles.—History, observer present

Takes an appropriate history (per observer checklist) from an adolescent with swollen ankles

Demonstrates appropriate interviewing skills (per observer checklist)

Arrives at acute glomerulonephritis as the most likely diagnosis

Recommends appropriate investigation

Lists at least three possible complications

Stations 15 and 16, Wheezer.—History, observer present

Takes an appropriate history (per observer checklist) from the mother of a child with "frequent" infections

Uses appropriate interviewing skills (per observer checklist)

Arrives at the most likely diagnosis and gives a differential

Offers reassuring explanations

Stations 17 and 18, Rest Stations

Stations 19 and 20, Facies.—Physical examination, no observer

Detects and describes at least nine of the 15 distinct abnormalities in general physical examination in this child with fetal alcohol syndrome

Arrives at a differential diagnosis

Table 1.—Contents of the OSCE* (cont)

Stations 21 and 22, Smear.—Laboratory, no observer

Uses a microscope appropriately

Detects four of the six abnormalities in the morphologic features of the blood smear

Proposes four of the six possible differential diagnoses

Orders at least three other necessary hematologic tests and avoids invasive ones (eg, bone marrow)

Stations 23 and 24, Tachycardia.—Laboratory, no observer

Given before-and-after ECGs, makes a diagnosis of supraventricular tachycardia in a newborn

Points out at least four ECG characteristics that differentiate this from a ventricular tachycardia

Proposes at least three means of emergency treatment (avoids use of verapamil)

Stations 25 and 26, Heart Murmur.—Physical examination, observer present

Performs an appropriate cardiovascular examination (per observer checklist)

Detects and records at least five normal or abnormal pertinent physical signs in this patient with a VSD

Makes a correct diagnosis of VSD, including assessment of the size of shunt

Answers questions on hemodynamics and prognosis for this child

Stations 27 and 28, Rest Stations

Stations 29 and 30, Anemia.—Physical examination, observer present

Performs an appropriate general physical examination on a child with anemia and hepatosplenomegaly (per observer checklist)

Detects and records at least five of the eight major abnormalities on physical examination

Arrives at a differential diagnosis

Answers questions on possible complications and on recommended treatment for this patient

Stations 31 and 32, Alte.—History, observer present

Takes an appropriate history (per observer checklists, process and content) from the mother of an infant who "stopped breathing"

Lists at least two items from the history that suggest a significant occurrence

Answers questions on epidemiology, pathogenesis, management, and follow-up of this infant

Stations 33 and 34, FTT.—History, observer present

Given a 9-month-old infant with FTT, takes a focused history from the mother (per observer checklists for process and content)

Makes a differential diagnosis

Writes hospital admission orders

Stations 35 and 36, Rest Stations

Stations 37 and 38, Chart Review.—No observer; given a copy of the history and physical examination on a 12-year-old boy with abdominal pain

Lists information missing in the history

Lists information missing in the physical examination

Assesses the overall quality of the document

Stations 39 and 40, Stridor.—Laboratory station, no observer; given roentgenograms of the upper airway in a child with stridor

Describes the radiologic findings

Offers the most likely diagnosis

Outlines a plan of management

Stations 41 and 42, Cough.—Laboratory station, no observer; given chest roentgenograms of a 2-year-old child with lobar consolidation and atelectasis of the left lung

Describes the radiologic findings

Gives the reason(s) for mediastinal shift

Predicts the physical findings in the chest

*OSCE indicates Objective Structured Clinical Examination; IVP, intravenous pyelogram; ECG, electrocardiogram; VSD, ventricular septal defect; and FTT, failure to thrive.

program. The following hypotheses were formulated: (1) residents at an advanced level of training would score higher than the more junior residents and students (*construct validity*); (2) there would be a low but acceptable correlation between the OSCE scores and the results of the monthly resident evaluation (*concurrent validity*); and (3) residents would agree that the OSCE is a better measure of clinical competence than the other methods used (*content validity*).

METHODS

The Planning Process

A task force composed of five full-time faculty and the two chief residents created a blueprint for the examination. Selection of problems was guided by the written program objectives and according to such considerations as prevalence, priority, availability, practicality, and adequate sampling.

The Stations

Forty-two stations were created as follows: there were 17 stations for performance of a variety of well-defined clinical tasks, 17 were for answering questions, and eight were rest stops. The clinical tasks were six interviews, four physical examinations, one chart review, and six laboratory tests. In the interview sections, there were two real patients with their mothers (recurrent respiratory infections and familial hypercholesterolemia, respectively) and four simulated ones (the "mother" of an infant with failure to thrive and another of an infant with apnea, a teenager with a history of swollen ankles, and a lying-in nurse attending a mother in the process of having a cesarean section). For physical examination there were real patients with hearing loss in one ear, fetal alcohol syndrome, ventricular septal defect, and hepatosplenomegaly with anemia. In three of the laboratory stations, there were roentgenograms of patients with pneumonia, upper airway obstruction, and rickets. In one, there were before and after conversion electrocardiograms of supraventricular tachycardia and in another, there was a microscopic slide of a blood smear of a patient with hypochromic microcytic anemia. In the sixth and last laboratory station, there were results of a urinalysis, slides of urinary sediment, and roentgenograms of an intravenous pyelogram in a patient with pyelonephritis. In the chart review station, an actual history and physical examination on a patient with abdominal pain was reproduced and the resident was directed to point out its deficiencies. Table 1 shows more details on the contents of the evaluation.

Patient Selection and Preparation

Pediatric clinic patients with stable physical findings and cooperative dispositions were invited to participate. An attempt was made to find duplicate patients to provide relief. For two of the four physical examinations, duplicate patients with identical findings were found. For the third, a sister of the patient with hearing loss was taught to simulate a conduction hearing loss in one ear. She was coached and tested repeatedly and learned to be consistent in her responses. The examination of the patient with fetal alcohol syndrome required mainly inspection only and an alternative was not thought necessary. For this initial trial, there were no plans to formally assess the reliability of patients or interviewees, but every attempt was made to ensure a level of consistency. Of the total of 13 individuals used (four as duplicates), five had stable physical findings and two were mothers of patients with chronic disorders (hypercholesterolemia, frequent infections). Only six had to learn a scenario. Three of these were trained nurses simulating a lying-in nurse, the mother of a child with failure to thrive, and the mother of an infant with "apnea." The fourth was the sister of a girl with conduction hearing loss who simulated the condition and the last two were sisters simulating a history of swollen ankles and dark urine. All the patients, real or simulated, were given salient features of their case histories in writing and were asked to memorize them. They were instructed not to volunteer the information unless specifically

asked. For unanticipated questions, they were to supply their own real-life experiences. Designers of each of the stations held frequent practice sessions in person or by phone until they were assured of a reasonable degree of consistency. Thus, given the stability, experience, and the background of the patients, it was believed that the interresident variability of the encounters would be minimized. Each patient or family was paid \$50 as an honorarium.

Checklists and Rating Scales

For each of the history-taking and three of the examination stations, an observer checklist was developed that listed all the expected questions to be asked and maneuvers to be performed. The planning group agreed on a score for each item. An observer rating scale was similarly constructed to evaluate the process of the encounter. Finally, a rating scale was produced for the patient to assess the resident interaction and general approach.

Test Questions

For each of the 17 halfway stations, a set of written questions was prepared. These were composed of open-ended, short-answer, and multiple-choice questions. The latter had one or more correct answers with negative marks for incorrect ones. A serious attempt was made to avoid trivial questions and to concentrate on meaningful outcomes related to the case at hand. For each question, all expected answers were written out and a score was assigned for each. Finally, a minimum pass level was derived for each station. All of this work was done by committee consensus.

Resident and Observer Orientation

Two weeks before and again on the morning of the examination, a three-page orientation handout was discussed with the residents and their questions were answered. In addition to an explanation of the test procedures, they were cautioned to do exactly what was asked of them and no more. They were told to describe to the observer what they were doing and what they were finding in the physical examination stations. Otherwise they were to have no interaction with the observers. Each resident was given a sufficient number of name tags to affix to all the various rating scales and answer sheets. Another orientation handout was produced and mailed to the observers and was discussed as a group on the morning of the test. Each observer was expected to learn two stations.

The Test Administration

The examination, given over a 4½-hour period, took place in a single large hall on Saturday morning, April 7, 1990. There were enough examining rooms for each patient encounter and laboratory station. Desks and chairs were set up outside each room for answer stations. Five minutes were allowed for each station and 1 minute was allowed for changeovers. The timekeeper announced each round by a shrill whistle. At the start, one half of the residents entered the odd-numbered stations, including rest stops, while the other half waited their turn. As the first group emerged to answer their questions, the second group took their places. Runners continually collected answer sheets, rating scales, and checklists as soon as they were completed. These were then checked against a master list and filed. To avoid fatigue, three observers worked on two stations. Each rotated after four rounds in one station and took a four-round rest after eight rounds of work. Similarly, physical examination patients rotated every four rounds. Schedules were made for each patient and observer to indicate where he or she was expected to be at each round. A running count of the rounds was kept on a flip chart.

Resident Feedback

At the end of the session, each resident anonymously filled out a form evaluating the process and content of the examination. There were seven Likert-type questions with five scales ranging from "strongly agree" (5) to "strongly disagree" (1). In addition, there were three open-ended questions asking about problems

Table 2.—Analysis of Variance of the Scores Grouped According to the Level of Training*

	Students	PL-1	PL-2	PL-3	F	P
OSCE†	102	136	151	166	13.5	.000
ITE‡	...	50	57	68	11.06	.000
RPR§	...	3.71	3.79	4.29	3.85	.035

*PL-1 indicates first-year postgraduate level; PL-2, second-year postgraduate level; and PL-3, third-year postgraduate level.

†Group means of the sum of all station scores; OSCE indicates objective structured clinical examination.

‡Group means of percent correct; ITE indicates in-training examination.

§Group means of 1 year of ratings, scales 1 to 5; RPR indicates resident performance rating.

during the test, organization of the test as a whole, and overall impression.

Other Test Scores Used for Comparison

There were two other scores for comparison: resident performance ratings (RPRs) are five-point Likert-type rating scales that are completed monthly by attending physicians and by chief residents. They consist of sections assessing attitude, interpersonal relationship, clinical judgment, knowledge base, and technical skills. During the last year, each of the three hospitals' Evaluation Subcommittees met at the end of each month's rotation and compiled an overall rating that was then forwarded to the program Evaluation Committee. Participation of nursing staff was considered a significant improvement in the process. For the purpose of this study, the overall scores for the ratings of the previous year were averaged and used in the comparisons. The other test scores were those of the American Academy of Pediatrics ITE which all but three of the residents had taken the previous July.

Data Management

All answer sheets, rating scales, and checklists, including resident evaluation of the examination, were corrected by hand. All scores for each station were converted to a proportion of the maximum score that ranged from 8 to 12 based on a differential weighting system. The data were tabulated and summed in various ways using a spread sheet program. A statistical program was used to calculate one-way analysis of variance, Pearson Product-Moment and Spearman Rank-Order correlations, and α -reliability coefficient. The OSCE scores of various groups of examinees were compared with each other and with their scores in the other tests available. The level of statistical significance was taken to be P less than .05.

RESULTS

Table 2 shows the results of one-way analysis of variance of the total OSCE scores of the four groups of trainees. The residents' scores in their ITE and results of their monthly RPR are also shown. The Student-Newman-Keul method for comparison testing showed significant ($P < .05$) differences among all four groups in the OSCE scores, with scores being higher in groups with greater clinical experience. This attests to the construct validity of the OSCE. The ITE scores differed significantly between first-year postgraduate level (PGY-1) and third-year postgraduate level (PGY-3) residents, and between second-year postgraduate level (PGY-2) and PGY-3 residents, but not between PGY-1 and PGY-2 residents. The RPRs could distinguish only PGY-1 and PGY-3 residents.

Table 3 shows the results of Pearson Product-Moment correlations among OSCE scores, ITE scores, and RPRs of all the residents taken together. The correlation is strong between OSCE and ITE and between ITE and RPR, but is weaker between OSCE and RPR. This indicates that OSCE measures some of the same objectives measured by ITE

Table 3.—Correlations Between OSCE, ITE, and RPR*

	OSCE	ITE	RPR
OSCE	1
ITE	0.71 ($P < .001$)	1	...
RPR	0.41 ($P < .05$)	0.61 ($P < .001$)	1

*OSCE indicates objective structured clinical examination; ITE, in-training examination; and RPR, resident performance rating.

Table 4.—Results of Resident Evaluation of the Examination*

Questions	Mean Score
1. The OSCE measured important outcomes not measured by other tests	4.1
2. It should be a regular part of resident evaluation	3.8
3. The distractions prevented achievement of OSCEs goals	3.2
4. I felt intensely involved in most of the stations	4.0
5. The patients and the historians were realistic	4.2
6. The laboratory stations were useful and should be continued	3.8
7. It was an enjoyable experience	4.1

*The scales are from 1 (strongly disagree) to 5 (strongly agree). OSCE indicates objective structured clinical examination.

Table 5.—Correlations Between Subsections of OSCE*

	Total Score	History	Physical	Laboratory
Total score	1
History stations	.88	1
Physical examination stations	.85	.81	1	...
Laboratory stations	.85	.81	.76	1

*Pearson product-moment correlations, $P < .0001$ in all instances; OSCE indicates objective structured clinical examination.

and RPR. These tests were not given simultaneously but were close enough in time to still be considered a measure of concurrent validity of the OSCE.

Thirty-two (94%) of 34 participants completed the anonymous resident evaluation forms. Results are shown in Table 4. As can be seen, the reactions were strongly positive. In retrospect, more than one item should have been negatively worded (item 3), but the distractions of this complex examination were of special concern to the planners who wished to highlight it. In any event, the open-ended questions invited negative comments by asking for problems with any of the stations. In the section asking for "overall comments," eight residents volunteered statements about the relevance of the examination to clinical evaluation. When asked about the organization of the event, 23 (92%) of the 25 who answered the question had

laudatory comments about the smooth running of the examination despite this being a first-time experience for all. There were remarkably few complaints about the individual stations. Three residents needed more time in stations requiring psychosocial histories, while one resident felt 5 minutes was too long for each station. Two residents felt time pressures in answering questions and one would have preferred videotapes to slides of the newborn. On the whole, the resident's reaction can be taken as evidence for content validity of the OSCE.

Reliability of the examination was tested in different ways. Using each station as a test item, coefficient α was calculated to be .80. Using this figure, SE of measurement for the total OSCE score was calculated as ± 12.2 points (mean \pm SD) for the total group, 139.3 ± 27.2 ; range, 88 to 191). Next, dividing the stations into two equivalent halves based on what was being measured, a split half reliability index of 0.83 was obtained. Finally, Table 5 shows correlations between scores derived for subsections of the OSCE (history, physical, and laboratory stations). All of this can be taken to indicate good reliability for the test as a whole.

COMMENT

Evaluation is a powerful determinant of student learning. Alterations in examination methods have been shown to change both learning and teaching behaviors.^{18,19} Unfortunately, as most often practiced, examinations are also the weakest link in the educational process. In the United States, most formal examinations in medicine mainly test cognitive objectives of lower taxonomic orders. Yet Altmaier et al,^{20,21} in studies involving pediatric and obstetric residents, found that only 20% to 30% of critical incidents selected as defining successful performance among residents were cognitive in nature; the remainder dealt with attitudes, communication skills, and interpersonal relations. These latter attributes are presumably measured by performance ratings, the most prevalent mode of evaluation in postgraduate training.²² Yet these ratings generally have low reliability (subjective assessment, poor interrater relationships, central tendency) and poor validity (the halo effect, influence of irrelevant attributes, and rating of skills never directly observed).²³ Studies correlating these subjective ratings with measures of clinical competence have yielded poor results.^{13,24-26}

Thus, the emerging trend toward measuring more meaningful educational objectives is a welcome development. The task is difficult but the rewards are plentiful once the inertia is overcome. This initial attempt at clinical evaluation in our program was the high point of the academic year. The willingness of the parents and the older children to get involved (there were more volunteers than needed and no cancellations) was gratifying. The smooth running of the test was remarkable and the few glitches were taken in stride and in good humor. The much-feared problems of using children in an OSCE did not materialize. The total out-of-pocket cost was less than \$2000 (\$57 per examinee), not counting faculty and staff time. This compares with \$140 per student in a performance-based assessment of clinical skills in 72 senior students⁸ and with an estimated \$200 per medical resident in a full-day OSCE that used standardized patients.¹² The latter figure included administrative, developmental, and other costs. No cost figures are available for our RPR. The standard charge for the pediatric ITE has been \$30 per resident.

The main purpose of this study was to check validity and reliability of the test. The rise in OSCE scores with increasing levels of training supports construct validity for the examination. The fact that the ITE did almost as well in separating the years of training (could not distinguish between PGY-1s and PGY-2s) and showed good overall correlation with the OSCE scores indicates that these two tests measured some of the same objectives. The RPR did less well: it could only distinguish PGY-1s from PGY-3s. This is understandable. Aside from the inherent weaknesses of the rating process alluded to above,²² residents tend to be compared with those in the same year of training rather than with those above or below. In any case, the good overall correlations among OSCE, ITE, and RPR (Table 3) can be taken as evidence for concurrent validity of the OSCE. The reactions of the residents and students were encouraging and supported the content validity of the examination.

Tests measuring clinical competence suffer from low reliability. The more objective nature of the OSCE and a wider content sampling are expected to improve reliability. The reliabilities obtained on this examination were quite respectable and on a par with multiple-choice questions in other "objective" examinations. The relatively good correlations found in the present study between OSCE and the other more established examination methods (ITE and RPR) should not lead to the conclusion that these tests are equivalent and the introduction of infinitely more complex and difficult OSCE is not necessary for resident evaluation. The great advantage of OSCE and other tests directly measuring clinical competence is in the strong message conveyed to the learners of what the program values as important and desirable outcome of their education. It is not the ability to memorize details that is valued but the ability to gather data, analyze it, and make justifiable conclusions, all attributes of the skillful physician.

I gratefully acknowledge the immense amount of time, energy, and talent that were unstintingly given by the members of the OSCE Task Force (Ratnakar Kini, MD, Gregory Preston, MD, James Noble, MD, Homer Ryan, MD, Mirta Soler, MD, and Ramesh Sachdeva, MD) to the preparation and administration of this examination. Special thanks go to Michael Campbell for assistance in data processing and to Toni Kincannon for preparation of the manuscript.

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John T. Flynn, MD

(*Arch Ophthalmol.* 1991;109:785)

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Sheila K. West, PhD; Nathan Congdon, MPhil; Sidney Katala, NO;

Lisa Mele, ScM

(*Arch Ophthalmol.* 1991;109:855-857)

ARCHIVES OF DERMATOLOGY

The Laboratory Diagnosis of Lyme Disease

Daniel Berg, MD; Kim G. Abson, MD; Neil S. Prose, MD

(*Arch Dermatol.* 1991;127:866-870)

A is for Amphetamines

Patients abusing stimulants may present with the following symptoms: excessive talkativeness, irritability, paranoia, palpitations, and chest pain. Sequelae of stimulant abuse include cardiac arrhythmias, convulsions, and stroke.¹



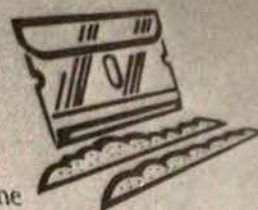
B is for Barbiturates

The barbiturate abuser may present with stupor, slurred speech, and loss of equilibrium. Sequelae include depressed respiratory functioning, heart failure, pneumonia, and convulsions.¹



C is for Cocaine

Cocaine abusers present with many of the same symptoms and sequelae seen with other stimulant abusers.¹ But also watch for a chronic snuffle and inflammation of the nasal mucosa. Chronic cocaine inhalation can lead to destruction of the nasal septum.¹ And intravenous use of all drugs can lead to HIV infection.



D is for Death

The ultimate sequela.



Educate Your Patients about the Effects of Drug Abuse

Partnership for a Drug-Free America

Education is the Best Antidote

Effects of Obesity on Aerobic Fitness in Adolescent Females

Thomas W. Rowland, MD

● Obesity impairs performance in most athletic events, but the influence of increased body fat on cardiopulmonary function has not been clearly delineated. An understanding of the fatness-fitness relationship is important in the optimal design of exercise programs for obese subjects. In this study, 27 adolescent females with body fat levels ranging from normal to gross obesity were evaluated to determine the impact of adiposity on physiologic factors during maximal and submaximal treadmill walking. Increased skinfold measures correlated significantly with absolute maximal oxygen uptake throughout the range of body fat levels ($r = .72$), and oxygen consumption per kilogram of body weight and treadmill endurance time both declined as fatness increased ($r = -.49$ and $-.42$, respectively). Obesity did not affect submaximal walking economy. These findings indicate that increased fat levels are associated with increased cardiopulmonary exercise capacity, but that functional fitness declines because of the inert load created by excess body fat. Therefore, therapeutic exercise programs for obese adolescents are best designed to increase caloric expenditure and decrease body fat rather than to improve aerobic fitness. (AJDC. 1991;145:764-768)

Excess body fat may be significantly detrimental to exercise performance, particularly in activities requiring propulsion or lifting of body weight.¹⁻⁵ Increased body fat content has been consistently reported to relate inversely to performance in events such as distance runs, sprints, pull-ups, and broad jumping regardless of age, sex, or athleticism. Watson's study of adolescent boys² indicated that a 46-yard decrement in distance covered in a 12-minute walk-run might be expected for each 1% increase in body fat. Boileau and Lohman³ showed that if age, height, and weight of children were statistically constant, a decline from the 10th to 35th percentile in mile-run performance occurred when the percentage of body fat increased from 15% to 30%.

Several explanations have been offered for this negative relationship between fitness and fatness: (1) Body fat may be simply an inert load during weight-bearing activities.^{6,7}

According to this concept, cardiopulmonary responses to exercise are normal in obese individuals, and exercise performance is compromised by the extra "baggage" that needs to be transported. (2) Excessive body fat may interfere with normal cardiac and pulmonary function and limit maximal aerobic responses to high-exercise loads.^{8,9} If so, physical capabilities in obese subjects are reduced at least partially by direct reduction of cardiopulmonary reserves during exercise. (3) Ventilatory function may be compromised by excessive body fat and thereby limit aerobic capacity. Obesity has been reported to diminish pulmonary compliance, decrease the efficiency of the ventilatory muscles, and decrease lung vital capacity.^{10,11} (4) Cardiovascular fitness may be depressed by the sedentary life-style adopted by the obese individual.¹² Reduced exercise capability in this case is secondary to a decline in maximal aerobic power no different than that of any individual not engaging in normal amounts of physical activity.

An understanding of alterations in cardiopulmonary responses to exercise in obese subjects bears practical importance. If adiposity causes depression of cardiovascular fitness, measured as the maximal oxygen uptake ($\dot{V}O_{2\max}$) therapeutic exercise programs for obese individuals should be designed to conform to guidelines of frequency,

Department Editors.—William B. Strong, MD, Augusta, Ga; Carl L. Stanitski, MD, Pittsburgh, Pa; Ronald E. Smith, PhD, Seattle, Wash; Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—The National Health Promotion and Disease Prevention Objectives that have been enunciated in the 1991 edition of Healthy People 2000 include physical activity and fitness as well as nutrition. One of the major goals of these two objectives, especially among the young, is to reduce the prevalence of obesity. Both physical activity and nutrition interventions are necessary. This article documents the importance of physical activity as the major source for caloric expenditures and weight reduction.

—W.B.S.

Accepted for publication January 28, 1991.

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Anthropometric and Physiologic Comparisons of Obese and Nonobese Subjects*

	Obese Subjects (n = 14)	Nonobese Subjects (n = 13)
Age, y	16.2 ± 1.8	16.4 ± 1.0
Weight, kg	76.5 ± 16.6	51.8 ± 6.8 [†]
Height, cm	159 ± 6	157 ± 5
Skinfold sum, mm	63.9 ± 14.9	29.7 ± 6.0 [†]
Submaximal exercise [‡]		
\dot{V}_{O_2}		
L/min	1.98 ± 0.35	1.40 ± 0.17 [†]
mL/kg per minute	26.1 ± 1.8	27.0 ± 1.3
\dot{V}_E		
L/min	63.5 ± 14.2	46.1 ± 6.5 [†]
mL/kg per minute	0.84 ± 0.11	0.89 ± 0.08
HR, beats/min	182 ± 14	178 ± 14
Oxygen pulse, $\dot{V}_{O_2}/HR \times 10^3$	10.8 ± 1.7	7.9 ± 1.2 [†]
Breathing rate, breaths/min	46 ± 9	41 ± 8
Breathing rate: tidal volume	33.3 ± 9.3	38.0 ± 14.8
\dot{V}_E/\dot{V}_{O_2}	32.09 ± 4.02	32.98 ± 3.39
Maximal exercise [‡]		
Endurance, min	8.1 ± 2.4	10.9 [†] ± 3.6 [†]
\dot{V}_{O_2}		
L/min	2.16 ± 0.36	1.71 ± 0.30 [†]
mL/kg per minute	29.2 ± 3.8	33.1 ± 4.7 [†]
RER	1.05 ± 0.05	1.02 ± 0.05 [†]
\dot{V}_E		
L/min	77.4 ± 13.6	64.8 ± 15.0 [†]
mL/kg per minute	1.03 ± 0.19	1.25 ± 0.25 [†]
HR, beats/min	190 ± 11	197 ± 11
Oxygen pulse, $\dot{V}_{O_2}/HR \times 10^3$	11.3 ± 1.8	8.7 ± 1.5 [†]
Breathing rate, breaths/min	52 ± 8	51 ± 9
Breathing rate: tidal volume	33.1 ± 13.0	38.3 ± 16.9
\dot{V}_E/\dot{V}_{O_2}	36.17 ± 4.53	37.84 ± 5.65
Ventilatory threshold		
mL/kg per minute	18.6 ± 2.0	20.8 ± 2.1 [†]
% of \dot{V}_{O_2} max	63.6 ± 6.1	66.4 ± 7.0

*Subjects were considered obese if the sums of their tricep and scapular skinfold measurements were above the 90th percentile. Values are means ± SDs. \dot{V}_{O_2} indicates oxygen consumption per unit of time; \dot{V}_E , expired volume per unit of time; HR, heart rate; RER, respiratory exchange ratio; \dot{V}_{O_2} max, maximum oxygen consumption.

[†] $P < .05$ for obese vs nonobese subjects.

[‡]Submaximal exercise was performed on a treadmill with an 8% grade at 5.2 km/h. Maximal exercise was performed at the same rate with 2% increases in grade every 3 minutes until exhaustion.

duration, and intensity necessary to improve aerobic fitness.¹³ If a decrease in cardiopulmonary function is not characteristic of obesity, exercise programs may be of lower intensity sufficient to increase caloric output. The distinction is important, because limiting exercise intensity in managing obese patients is considered a valuable means of improving subject compliance.¹⁴

This study investigates the effects of obesity on cardiopulmonary function during exercise in a group of low-fit

adolescent females. Specifically, information was sought concerning the relationship of adiposity and markers of maximal aerobic function, submaximal indicators of aerobic fitness (heart rate, walking economy, and anaerobic threshold), and patterns of ventilation, particularly as they relate to breathing efficiency. These factors were examined in subjects representing a continuum of body fat levels from normal to grossly obese to determine if the degree of fatness affects the qualitative features of the cardiopulmonary response to exercise.

SUBJECTS AND METHODS

Twenty-seven female high school students were recruited for treadmill testing from a physical education class designed for individuals with self-perceived low levels of physical fitness. The mean age of the subjects was 16.5 years (SD, 1.0 year; range, 15.3 to 18.8 years). None suffered chronic disease or were acutely ill at testing. All denied smoking cigarettes, and there was no history of use of medications that would affect exercise performance. Fourteen of the students were included in a previous report¹⁵ describing the effects of walking training on aerobic fitness.

Informed consent was obtained from the parents of all subjects. This study was reviewed and approved by the research review committees of the Baystate Medical Center, Springfield, Mass.

Measures of cardiopulmonary fitness were recorded during a maximal treadmill walking test. Height and weight were determined before testing, followed by calculation of body mass index (BMI, weight divided by square of height). The BMI correlates well with other indexes of obesity; a value of 24 is believed to be the upper limit of "desirable" body fat, and a BMI of 29 indicates approximately 20% overweight.¹⁶ Triceps and subscapular skinfolds were measured using a skinfold caliper (Holtain, Crosswell, England) that provides a constant pressure of 10 g/mm². Three values were obtained from the right side of the body using standard techniques.¹⁷ The mean values were summed to create a skinfold score. This score has been shown to correlate with body density (and, thus, with body fat content) in obese and nonobese adolescents, with correlation coefficients of .77 to .95.^{18,19}

Progressive, continuous treadmill walking was performed to exhaustion in an air-conditioned laboratory (20°C to 22°C). The subjects were acclimated to the treadmill with a 2-minute warm-up walk at 4.8 km/h with no grade. The initial treadmill slope was 6%, which was increased 2% every 3 minutes. A speed of 5.25 km/h was maintained, and subjects exercised until voluntary exhaustion. Grasping of handrails was not permitted except transiently during gradient changes. At peak effort, all subjects demonstrated hyperpnea, facial flushing, sweating, and unsteady gait as well as either respiratory exchange ratio of more than .98 or heart rate exceeding 190 beats per minute.

Heart rates were determined electrocardiographically during the final 30 seconds of each stage and at maximal exercise. Gas exchange values were measured using standard open-circuit techniques using a computerized metabolic cart (Q-Plex Cardiopulmonary Exercise System; Quinton Instrument Co, Seattle Wash). Subjects breathed through a 94-mL dead-space Rudolph valve, and minute ventilation was determined using a pneumotachometer in the expiratory line. Expired gas samples from a mixing chamber were analyzed for oxygen and carbon dioxide concentration using zirconia oxide and infrared analyzers, respectively. Data were averaged every 15 seconds, and used to calculate oxygen uptake, carbon dioxide output, expired ventilation (\dot{V}_E), ventilatory equivalent for oxygen (\dot{V}_E/\dot{V}_{O_2}), respiratory rate, tidal volume, and respiratory exchange ratio. The system was calibrated before each session with standard gases of known oxygen and carbon dioxide concentrations.

Maximal values of gas exchange parameters were defined as the mean of the two highest recordings during the final minute of exercise. Submaximal values were defined as the mean during the final minute of the second stage (5.2 km/h and 8% grade).

Confusion exists concerning the proper expression of physical

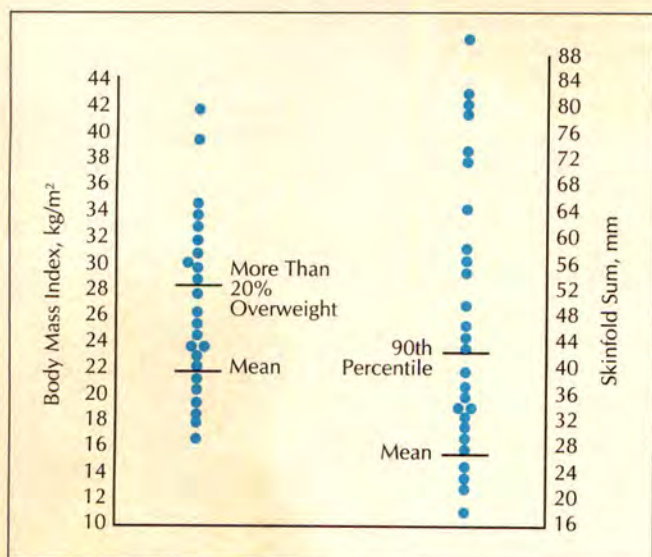


Fig 1.—Body mass index and skinfold scores (triceps and scapular sum) of the 27 subjects.

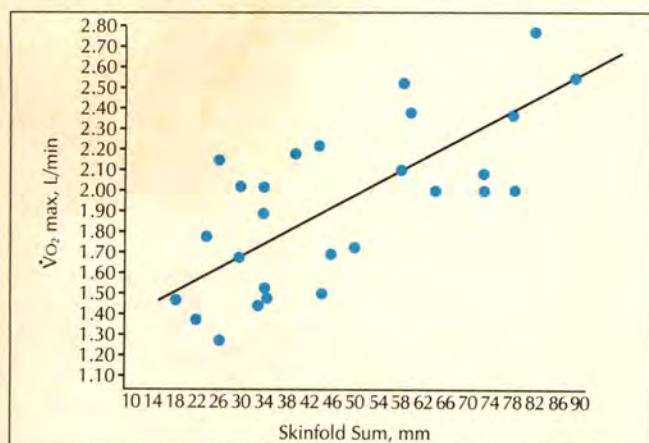


Fig 2.—Relationship of body fat, as indicated by sum of triceps and scapular skinfold thickness, and absolute maximal oxygen uptake ($r = .72$, $P < .01$, and $y = 1.33 + .014x$).

fitness of obese subjects, and definition of terms is important. In this study, absolute aerobic fitness denotes physiologic characteristics independent of body weight or composition and is indicated by measurement of oxygen uptake. Oxygen consumption is an expression of the product of cardiac output and arteriovenous oxygen difference, but several factors, including pulmonary and hematologic factors and muscle disease, can limit maximal oxygen uptake.¹² Functional aerobic fitness is the maximal oxygen uptake relative to body mass ($\dot{V}O_2\text{max/kg}$ of body weight), a critical determinant of exercise capacity or performance, which refer to capabilities in physical activities (such as 1-mile run time).

Walking economy was defined as the gross oxygen cost of moving 1 kg of body mass at a given submaximal treadmill setting. The maximal and submaximal oxygen pulse ($\dot{V}O_2/\text{heart rate}$) was examined as an indicator of absolute cardiovascular fitness. Unfit individuals are characterized by a greater reliance on heart rate to increase $\dot{V}O_2$ (and lower oxygen pulse) than those who are fit.²⁰

Respiratory function during exercise was assessed using maximal and submaximal $\dot{V}E$, breathing rate, ratio of breathing rate to tidal volume, and ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$, an index of breathing efficiency). The ventilatory threshold was investigated as an indirect measure of anaerobic threshold. Ventilatory threshold was defined as the $\dot{V}O_2$ at the point of upward deflection of the ventilatory equivalent for oxygen without a con-

comitant rise in ventilatory equivalent for carbon dioxide. Ventilatory threshold was expressed as both $\dot{V}O_2/\text{kg}$ and percentage of $\dot{V}O_{2\text{max}}$ (which may reflect anaerobic capacity).²¹

Subjects were divided into obese ($n = 13$) and nonobese ($n = 14$) groups based a skinfold score above and below the 90th percentile (42 mm) for age, respectively.²² Anthropometric and physiologic values were compared between groups using an unpaired Student's t test. A simple Pearson's Product-Moment Correlation Coefficient analysis was conducted between skinfold scores of the two groups as a marker of obesity and maximal absolute and weight-relative oxygen uptake and treadmill endurance time. Statistical significance was defined as $P \leq .05$.

RESULTS

The perceived low level of physical fitness of the subjects was verified by depressed levels of $\dot{V}O_2\text{max/kg}$ (group mean, 30.9 mL/kg per minute; SD, 4.6; expected $\dot{V}O_2\text{max/kg}$, 40 to 45 mL/kg per minute).²³ Body mass index and skinfold scores compared with population norms are illustrated in Fig 1. A continuum of increased body fat was observed, with one half of subjects having BMI values exceeding the "desirable" range and more than one quarter having values above that estimated for 20% overweight.¹⁶ Eighty-one percent had skinfold scores exceeding the average expected for age and sex, and measurements in 13 (48%) were greater than the 90th percentile (42 mm).²² No association was evident between height and skinfold score ($r = .05$, $P = .8$). A correlation coefficient of .89 was observed between BMI and skinfold score.

Anthropometric and physiologic comparisons between the obese and nonobese groups during maximal and submaximal exercise are indicated in the Table. Maximal absolute oxygen uptake and ventilation were greater in the obese individuals, but were significantly less than those of the nonobese subjects when related to body weight. Corresponding to their lower $\dot{V}O_2/\text{kg}$, the obese subjects demonstrated 26% shorter treadmill endurance times than did the nonobese.

Increased body fat did not affect walking economy. Absolute values of submaximal $\dot{V}O_2$ were greater among obese subjects, but the oxygen uptake cost of moving body mass ($\dot{V}O_2/\text{kg}$) was not affected by increased body fat. Submaximal ventilation values paralleled those of oxygen uptake.

Submaximal heart rate was not affected by skinfold score. Increases in absolute $\dot{V}O_2$ to accommodate propelling larger fat mass at submaximal exercise levels were attributed to greater cardiac stroke volume and/or peripheral oxygen uptake. This is indicated by the significantly greater mean submaximal oxygen pulse value of the obese group.

Skinfold score was directly related to absolute $\dot{V}O_2\text{max}$ ($r = .72$, $P < .0001$), with a linear association through the extremes of adiposity in this group of subjects (Fig 2). However, increased obesity resulted in progressive deterioration of both $\dot{V}O_2\text{max}$ related to body mass ($r = -.49$, $P = .02$) and treadmill endurance time ($r = -.42$, $P = .03$). Therefore, subjects who were more obese had greater levels of absolute aerobic fitness but lower functional aerobic fitness and exercise capacity.

The obese subjects exhibited significantly higher oxygen pulses at maximum exercise, but obesity had no influence on maximal heart rate. As with submaximal exercise, the higher $\dot{V}O_2\text{max}$ values associated with greater obesity reflected larger maximal cardiac stroke volumes and/or peripheral oxygen extractions.

The influence of body fat on maximal absolute and weight-relative minute ventilation during treadmill walking paralleled those of oxygen uptake. Obesity did not affect breathing rate, breathing rate-tidal volume ratio, or breathing efficiency (\dot{V}_E/\dot{V}_{O_2}) at either submaximal or maximal levels of walking. Ventilatory threshold could be determined in 24 (89%) of the 27 subjects. Oxygen consumption at ventilatory threshold was significantly lower in the obese subjects, but excess body fat had no effect on ventilatory threshold expressed as percentage of $\dot{V}_{O_2\max}$.

COMMENT

Cross-sectional studies of obese adults have provided a consistent picture of the influence of adiposity on cardiopulmonary function during rest.²⁴⁻²⁸ The greater perfusion demands created by excess body fat are reflected in increased resting cardiac output. This response to adiposity is met entirely through increases in stroke volume; heart rate remains unchanged. This chronic elevation in stroke volume in the obese subject is reflected in ventricular enlargement and eccentric hypertrophy but normal myocardial function.

Until body weight becomes extreme (generally more than 135 kg), these hemodynamic changes are well tolerated.²⁵ With marked long-standing obesity, however, left ventricular function becomes impaired, resulting in increased end-diastolic pressure and clinical signs of hepatomegaly, peripheral edema, ascites, and dyspnea.^{25,29,30} Early investigators considered these changes secondary to the direct effects of fatty infiltration in and around the heart, but most now view such congestive signs as a reflection of chronically accelerated cardiac output.^{25,31} Complications of systemic and pulmonary hypertension (pickwickian syndrome) resulting from obesity may add to this cardiac compromise.

Interpretation of cardiovascular responses to excessive body fat during exercise is less certain. Buskirk and Taylor⁶ contended that "the presence of excess fat per se does not have any important influence on the capacity of the cardiovascular system to deliver oxygen to muscles under maximal performance conditions." Their study of adult men exercising on treadmills indicated that absolute $\dot{V}_{O_2\max}$ related directly to percentage of body fat, while $\dot{V}_{O_2\max}/\text{kg}$ decreased with increasing obesity.

Our results confirm this conclusion. Increased adiposity in our subjects was linked to several indicators of superior absolute aerobic fitness during exercise. Maximum oxygen uptake was directly related to body fat (independent of body height) in a continuum from lean to grossly obese subjects. Maximum minute ventilation increased parallel with $\dot{V}_{O_2\max}$ as obesity increased. While the obese subjects demonstrated more cardiopulmonary functional reserve, their functional aerobic fitness and exercise capacity were impaired. That is, the augmented $\dot{V}_{O_2\max}$ in these individuals was insufficient to compensate for the load created by excessive body fat, as indicated by lower values of $\dot{V}_{O_2\max}/\text{kg}$ and shortened treadmill endurance times.

Arteriovenous oxygen difference is typically similar among obese and nonobese individuals.²⁸ The greater peak oxygen pulse values in the obese subjects in this study implies that the subjects' augmented oxygen delivery reflects increased maximal stroke volume. Maximal heart rates were not affected by body fat in this study or in others,^{32,33} and resting left ventricular size as determined using echocardiography and roentgenographic es-

timation of heart volume have been reported to be greater in obese subjects even before puberty.^{19,34}

The higher submaximal oxygen pulse values of our obese subjects are typical of athletes and subjects following athletic training and presumably reflect improved myocardial efficiency.²⁰ The relationship between heart rate and \dot{V}_{O_2} during exercise differs between obese and nonobese subjects in the same manner as between athletes and nonathletes. Farebrother³⁵ commented that "it could be considered that obese are fitter, due to the training effect of carrying about the excess body weight, but this implies the change is beneficial. It seems better to regard it as just appropriate to a condition of increased demand on the myocardium."

The greater muscle mass typical of young obese subjects may also contribute to increased absolute $\dot{V}_{O_2\max}$.^{6,8,19,33} Sprynarova and Parizkova³⁶ observed changes in body composition and oxygen uptake during an obesity therapy program in a group of 11-year-old boys. Body weight, fat, and lean body mass all declined with treatment, but changes in $\dot{V}_{O_2\max}$ correlated only with those of lean body mass. Buskirk and Taylor⁶ showed no significant differences in $\dot{V}_{O_2\max}$ related to fat-free mass (reflecting muscle volume) among their subjects, who demonstrated a wide range of obesity.

At submaximal levels of exercise, adiposity did not affect the walking economy of subjects in our study. Oxygen consumption increased because of the need to move excessive fat, but \dot{V}_{O_2}/kg was not affected. This implies that at this intensity of exercise the many factors that contribute to the energy cost of treadmill walking (eg, gait kinematics, elastic recoil forces, and mechanical efficiency) were not influenced by the degree of obesity in these subjects.³⁷

Previous exercise studies of young obese subjects have provided conflicting data. Cooper et al³⁸ evaluated aerobic responses to exercise in obese children and adolescents by examining the ratio of maximal to resting oxygen uptake. The average among obese subjects was in the normal range, but six of 18 had values more than two SDs below the mean of nonobese subjects.

Zanconato et al³² performed maximal exercise testing on 23 obese children aged 9 to 14 years.³² Compared with lean control subjects, obese subjects demonstrated lower endurance times and $\dot{V}_{O_2\max}/\text{kg}$, but absolute $\dot{V}_{O_2\max}$ was not significantly different between the two groups. Huttunen et al³³ described similar findings among obese children and adolescents during exercise testing using cycle ergometers.

Other authors have reported a detrimental effect of obesity on cardiovascular function during exercise. Davies et al⁸ found that absolute $\dot{V}_{O_2\max}$ during treadmill testing of obese females aged 6 to 25 years was no greater than that of nonobese subjects. When $\dot{V}_{O_2\max}$ was related to lean body mass or leg volume, values were lower among obese subjects. These findings implied that fat is not simply an inert load but plays "some indirect role in the etiology of relative effort intolerance of the obese."

Dempsey et al⁹ reached the same conclusion in their study of obese young adult males exercising on cycle ergometers.⁹ At maximum exercise, no relationship between absolute $\dot{V}_{O_2\max}$ and percentage of body fat was observed, but a negative correlation existed between $\dot{V}_{O_2\max}$ and fat-free mass. The authors concluded that

"gross obesity—at least that in excess of 30% body fat—imposes a severe limitation on physical work capacity by its apparent interference with overall maximal cardiorespiratory function in addition to its burden as an inert, non-contributing load."

This study failed to identify any evidence of physiologic impairment due to obesity during maximal or submaximal treadmill walking in a group of adolescent girls with a wide range of body fat. On the contrary, obesity was associated with augmented cardiovascular and pulmonary function at maximal exercise. Reductions in relative aerobic fitness and exercise capacity appeared to result entirely from the effect of excess body fat acting as an inert load during weight-bearing activities. These results indicate that the problem for obese adolescents is not depressed aerobic fitness but rather insufficient increases in cardiovascular function to match the augmented load imposed by excessive body fat. Therefore, therapeutic exercise programs for obese teenagers would be best designed to increase caloric expenditure rather than improve aerobic fitness. Incorporation of activities to improve caloric energy output, which need not be at the high sustained intensity necessary to increase aerobic fitness, should help facilitate adherence to exercise programs for obese patients.

The author thanks Coleen Walsh, MS, and Meredith Varzeas, MEd, for their assistance with this study and Lee Cunningham, DPE, Paul Martha, MD, and Edward Reiter, MD, for their thoughtful reviews of the manuscript.

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Seasonal Variation in Growth During Growth Hormone Therapy

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● Seasonal variation in growth of normal children has been well described, although the mechanism by which it occurs has not been elucidated. The growth of 52 growth hormone-deficient children treated with synthetic human growth hormone was analyzed. A similar seasonal variation was observed, with mean (\pm SEM) peak growth occurring in the summer (8.2 ± 0.3 cm/y) and winter (7.7 ± 0.2 cm/y), and trough growth occurring in the autumn (6.9 ± 0.3 cm/y). Forty-seven percent of subjects grew minimally during the autumn, and only two children showed peak growth in that season. Individual variations between maximal and minimal growth seasons amounted to 3.5 ± 0.3 cm/y. The seasonal pattern was statistically significant for the group as a whole, for the prepubertal subgroup, and for the boys. The variation persisted when the first year of treatment was excluded to avoid bias of the initial growth spurt. The season of onset of therapy did not affect total growth during the first year. The demonstration of a seasonal pattern in growth of these children suggests that the seasonal variation may be mediated by peripheral rather than central factors. Paired clonidine-provoked growth hormone levels and an integrated concentration of 24-hour growth hormone levels and serum levels of insulinlike growth hormone I measured in a control group of normally growing children were also analyzed and showed no seasonal variation. This further suggests that peripheral rather than central factors are responsible for the seasonal variation in children's growth.

(AJDC. 1991;145:769-772)

Seasonal variation has been repeatedly, if not consistently, observed in the growth of normal children,¹⁻³ with variations in growth velocity between seasons amounting to as much as 5 cm/y.² The mechanism by which this seasonal variation occurs remains unclear.¹ No variation in growth hormone (GH) secretion through the year has been demonstrated,^{4,5} thus suggesting that peripheral rather than central factors are responsible for seasonal variation. We attempted to clarify retrospectively

the seasonal effect by analyzing the growth of GH-deficient children receiving constant-dose GH therapy. In addition, peak responses to clonidine-provoked testing and integrated concentration of daily GH profiles were also reviewed.

PATIENTS AND METHODS

Clinical Data

The medical records of 52 patients treated for GH deficiency at Rambam Medical Center, Haifa, Israel, and Kaplan Hospital, Rehovot, Israel, were reviewed. Patients had received a constant dose of 0.3 mg/kg of human GH recombinant (BioTechnology General Ltd, Rehovot, Israel) weekly in three divided doses from the onset of treatment for 24 to 33 months and were measured at 2- to 3-month intervals using Harpenden stadiometers. Based on the respective ratios of days in each season, growth velocities were calculated for each child for four 3-month periods corresponding to Israel's seasons, namely, March through May (spring), June through August (summer), September through November (autumn), and December through February (winter). Growth velocities for each season were compared by Student's *t* test. The data were then further analyzed as follows: (1) for each sex alone; (2) for those children who were pubertal or entered puberty during the study compared with those who remained prepubertal; (3) excluding the first year of treatment, to minimize bias of the initial growth spurt at the onset of therapy; (4) for a relationship between the season of start of treatment and growth in the first year; and (5) for the seasons in which each child demonstrated peak and minimal growth.

Laboratory Data

The integrated concentration of GH was studied in 82 normally growing children (54 boys and 28 girls; mean [\pm SD] age, 12.5 ± 3.0 years) as previously reported.⁶ Plasma insulinlike growth factor I (IGF-I) was measured before initiation of therapy, and at the end of 2 years of therapy in all 52 patients. These results were reviewed for evidence of a seasonal variation. Data were analyzed using the Kruskal-Wallis Test. In addition, GH response to clonidine (0.15 mg/m²) was analyzed in 82 children studied on two occasions in consecutive seasons. Results were analyzed using Student's paired *t* test.

RESULTS

Clinical Data

The medical records of 52 patients (39 boys and 13 girls) aged 5 to 17 years were reviewed. Thirty-five patients remained prepubertal throughout the study period of 24 to 33 months. The start of therapy was distributed throughout the year, as shown in Table 1. The total number of seasons of growth equaled 455.

Accepted for publication May 23, 1990.

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Table 1.—Effect of Season in Which Human Growth Hormone Therapy Was Initiated on the Growth of 52 Children During the First Year of Treatment

	Spring	Summer	Autumn	Winter
No. of children starting treatment	16	28	7	1
Height gain in first year, cm*	8.2 ± 0.5	8.2 ± 0.4	9.1 ± 0.6	9.2

*Values of height gain are mean ± SEM. Differences were not significant.

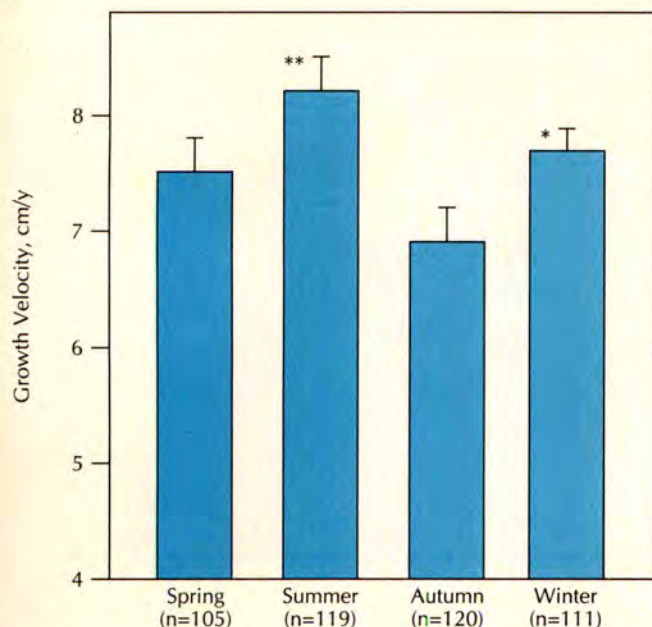


Fig 1.—Variation in growth velocity with season for 52 growth hormone (GH)-deficient children receiving human GH therapy for at least 2 years. The numbers in parentheses indicate the number of seasons of human GH therapy. Values are mean ± SEM. The asterisk indicates $P < .05$; double asterisk, $P < .005$ vs autumn.

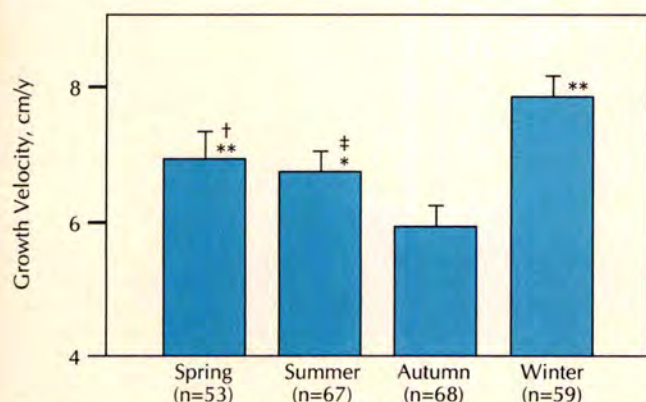


Fig 3.—Variation in growth velocity with season, excluding the first year of therapy, for 52 children treated with growth hormone. The numbers in parentheses indicate the number of seasons of growth. Values are mean ± SEM. The asterisk indicates $P < .05$; double asterisk, $P < .01$ vs autumn; dagger, $P < .05$; and double dagger, $P < .01$ vs winter.

Growth velocities for each season are shown in Fig 1. A seasonal variation was observed, with mean (±SEM) peak growth occurring in the summer (8.2 ± 0.3 cm/y) and, to a lesser degree, in winter (7.7 ± 0.3 cm/y). The lowest growth velocity occurred in autumn (6.9 ± 0.3 cm/y).

Figure 2 shows seasonal differences for the four sub-

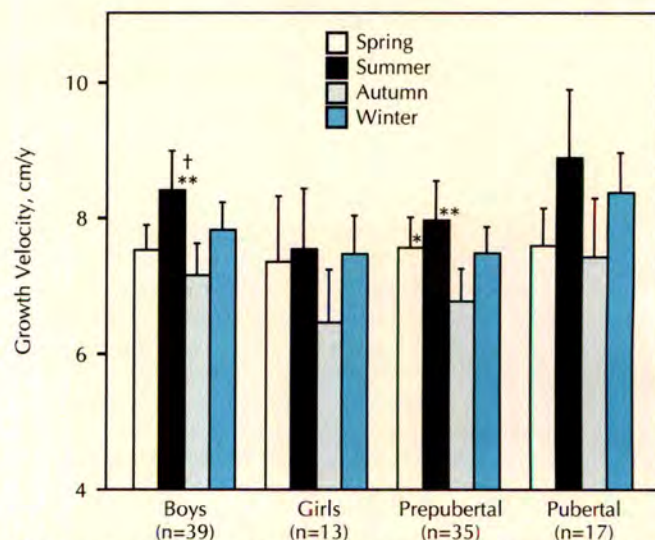


Fig 2.—Variation in growth velocity with season, according to sex and pubertal development, for 52 children treated with growth hormone who were studied for at least 2 years. Values are mean ± SEM. The asterisk indicates $P < .05$; double asterisk, $P < .01$ vs autumn; and dagger, $P < .01$ vs spring.

groups: male, female, prepubertal, and pubertal children. The pattern remained consistent for each subgroup, although it failed to reach statistical significance for the small number of girls and pubertal children in the study.

When the first year of therapy was excluded from the study, thereby reducing the influence of growth spurts occurring at the initiation of treatment, a seasonal variation was again observed, although the summer peak was blunted (Fig 3). The trough in autumn remained constant, however.

Table 2 shows the percentage of children demonstrating their peak and trough growth for each season, again excluding the first year of treatment. Only 8% of children had their peak growth in autumn, but 47% had their trough growth in this season. Seventy percent of children demonstrated their peak growth between December and May. These were significantly different from the expected 25% of children in each season (χ^2 analysis). The differences in growth velocity between maximal and minimal growth seasons amounted to 3.5 ± 0.2 cm/y for the group as a whole. No significant differences were seen in girls compared with boys or in pubertal compared with prepubertal children.

Finally, Table 1 shows the growth achieved during the first year of treatment as it related to the season of initiation of GH therapy. Small differences were observed between the groups, with those children starting treatment in autumn showing a slightly greater increment in growth. This, however, was not statistically significant.

Table 2.—Peak and Minimum Growth in Each Season of Children Receiving Human Growth Hormone Therapy (First Year of Treatment Excluded)

	Spring	Summer	Autumn	Winter
Children showing peak growth, %	34	22	8*	36†
Children showing minimum growth, %	22	27	47*	4*

* $P < .005$ of the expected 25%.† $P < .05$ of the expected 25%.**Table 3.—Mean (\pm SEM) Growth Hormone (GH) Secretion as Related to Season at Time of Testing**

	No.	Spring	Summer	Autumn	Winter	Spring
Clonidine-provoked GH levels, $\mu\text{g/L}$ *	24	14.9 ± 1.4	15.5 ± 1.4
	16	...	15.8 ± 1.4	16.4 ± 1.7
	27	14.1 ± 1.3	16.2 ± 1.4	...
	15	15.3 ± 0.9	15.4 ± 3.1
Integrated concentration of GH levels, $\mu\text{g/L}$ †	82	5.1 ± 0.5	4.9 ± 0.4	5.0 ± 0.3	4.9 ± 0.3	...
		(21)	(22)	(20)	(21)	...

*Clonidine-provoked GH response in subjects tested in two consecutive seasons. Differences were not significant.

†Integrated concentration of GH in 84 subjects tested in different seasons. No significant seasonal differences were found. Numbers in parentheses indicate numbers of tests.

Table 4.—Insulinlike Growth Hormone (GH) I Measurements in Pubertal Controls and GH-Deficient Children Receiving Human GH Therapy, as Related to Seasons*

	Spring	Summer	Autumn	Winter
Controls, U/mL	1.7 ± 1.2	1.6 ± 1.3	1.7 ± 1.3	1.7 ± 1.5
GH-deficient children, U/mL	1.9 ± 2.3	2.0 ± 1.6	1.7 ± 1.5	1.9 ± 1.5

*Values are mean \pm SEM. Differences were not significant.

Laboratory Data

In a control group of 84 normally growing children, no significant differences were found in results of repeated clonidine tests performed in consecutive seasons in the same patient (Table 3). Furthermore, no significant change in the integrated concentration of GH was found between seasons. No significant change was found between seasons in the IGF-I level of normal control children or of GH-deficient patients receiving GH therapy (Table 4).

COMMENT

Various studies carried out in California, England, and Ohio have demonstrated a seasonal variation in growth, with peak growth observed in spring to early summer and minimal growth in fall to early winter.¹⁻³ Previous studies failed to demonstrate variations in GH secretion, either in spontaneous profiles or on provocative testing,^{4,5} suggesting that the seasonal effect is not mediated by changes in GH secretion.

Results of the present study provide evidence that growth can substantially vary throughout the year, despite unchanging circulating levels of GH and IGF-I in children with GH deficiency treated with constant-dose GH.

This is at variance with a previous study in which GH was administered intermittently during the seasons.⁷ The pattern of growth in our study was remarkably similar to that described in normal children,¹⁻³ with peak growth occurring in summer, although we found that good growth also occurred in the mild Israeli winter months. Particularly consistent was the trough in growth occurring in autumn, which was observed in both the first and subsequent years of treatment, and in the usually more uniform growth in the prepubertal years, especially in boys.

This autumnal dip is of particular interest, given that 28 of the children started therapy in the summer. Accelerated growth is usually seen in the several months following initiation of treatment, and thus one would expect an artificially increased growth velocity in this season. This seasonal variation is further emphasized when the periods of peak and trough growth for each child are considered. The first year of growth was excluded to avoid bias of growth spurts at the start of treatment. In subsequent years, although children's peak growth was distributed through December to August, it is noteworthy that only two of our 52 children grew maximally between September and November. It is also striking that 47% of the children showed

minimal growth in autumn.

The degree of variation in growth between seasons was not insignificant. Although a mean difference of 1.3 cm/y was seen between autumn and summer for the group, individuals showed greater fluctuations in their growth, with a mean of 3.5 cm/y, and differences as high as 7.4 cm/y measured between minimal and maximal growth seasons.

The question whether the season in which GH treatment is initiated affects total growth in the important first year of treatment was also addressed. The group starting treatment in the autumn showed a marginally higher growth increment than the rest of the children. Thus, although children in this group did not have an autumnal dip, this did not significantly add to their total first-year growth.

It is difficult to hypothesize the mechanism by which the seasonal variation occurs. It has been shown that duration of sunlight does not cause fluctuations in GH secretion⁵; however, this does not exclude a role in seasonal growth through other means, since totally blind children grow with minimal growth periods distributed throughout the year.¹ Temperature, on the other hand, does not seem to be a factor since children showed a seasonal pattern of growth in California, where minimal changes in temperature occur throughout the year.¹ The mild climate of Israel is likewise unlikely to mediate seasonal variations.

The autumnal dip seems to have been consistent throughout these studies.¹⁻³ Autumn is a season in which differences in temperature and light are not extreme and therefore are unlikely to be responsible for the seasonal variation. It has been shown that seasonal variations in weight show the converse pattern to that of height.³ It is tempting to speculate that in late summer, when children tend to be more active and heat reduces appetites, weight gain is inadequate to promote good growth in the following season.

In concordance with previous studies, we did not demonstrate a seasonal variation in GH levels, either on provocation with clonidine or in integrated concentrations of GH; neither did we find that serum levels of IGF-I were affected by seasonal variations.

The observations in this study strongly suggest that variations in growth can occur independently of GH and IGF-I levels. Explanations for this phenomenon must invoke peripheral rather than central mechanisms; possibly an alteration in sensitivity of the end-organ or, alternatively, involvement of other hormones, such as androgens, which do vary throughout the year⁸ and which might augment GH activity.

Relative resistance to treatment with human GH has been described in emotionally deprived children: when endogenous GH secretion resumes, these children respond normally.⁹ Another point of special interest is the greater vulnerability of boys to the seasonal variations of

growth. We recently reported that boys are also more susceptible to psychological deprivation in terms of their physical growth.¹⁰ Whether the autumnal dip in growth rate and emotional deprivation share a similar mechanism is unknown.

Despite the fact that these fascinating aspects of growth are yet to be elucidated, important conclusions can be drawn from this study. First, evaluations of response to GH therapy cannot be made on short-term measurements, any more than they can be used in the evaluation of any child's growth.^{2,11} This is certainly true until the extent of seasonal variation is defined for any climatic area, and even then individuals seem to demonstrate considerable variation. This study also indicates that the season in which GH therapy is started does not seem to have a significant effect on the growth attained in the vital first year, although this should perhaps be reassessed with a larger group of children.

We thank Ruth Singer for her expert secretarial assistance.

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A Survey of Antiemetic Use in Children With Cancer

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• Pediatric oncologists within Pediatric Oncology Group institutions were surveyed to determine current antiemetic practices for children receiving chemotherapy and the basis for those practices. A mean severity rating for associated nausea and vomiting was calculated and used to rank 31 chemotherapeutic agents commonly used in the treatment of childhood cancer. Antiemetics were used 17%, 79%, and 98% of the time for chemotherapeutic agents with mild, moderate, or severe associated nausea and vomiting, respectively. A median of one, two, and three antiemetics were used for mild, moderate, and severe agents, respectively. Antihistamines and phenothiazines were the drugs most commonly used for agents causing mild or moderate nausea and vomiting, and metoclopramide hydrochloride/antihistamines with lorazepam and/or corticosteroids were used most often for chemotherapeutic agents causing severe nausea and vomiting. Most oncologists based their choice of antiemetics on personal experience. Current literature addressing the treatment of nausea and vomiting in children receiving chemotherapy, as reviewed here, does not always support the present clinical practices.

(AJDC. 1991;145:773-778)

Chemotherapy-related nausea and vomiting remains a major adverse side effect of cancer therapy despite an increasing number of available antiemetic agents. This is due in part to the increasing use of certain highly emetogenic agents such as cisplatin or high doses of cytarabine or cyclophosphamide. Pediatric antiemetic regimens have generally been adapted from those used in adults; however, the benefit-toxicity ratio may differ substantially in children compared with adults.¹ Although some of the antiemetic regimens have been tested specifically in children, many have not, and there is no general consensus regarding optimum antiemetic regimens for children receiving chemotherapy. In fact, the perceived need and usage of any antiemetics appears to vary substantially among pediatric oncologists. Differences in the potency of che-

motherapeutic agents and combinations of agents to induce nausea and vomiting are recognized but not quantified, contributing to the problem. A survey of pediatric oncologists and pediatric oncology nurses within the Pediatric Oncology Group (POG) was conducted to assess current uses of antiemetics for children receiving chemotherapy and the basis for decisions regarding choice of antiemetics. The results of that survey are presented in this article and compared with an earlier unpublished POG survey implemented in 1984, as well as with published reports of pediatric antiemetic trials. Behavioral and other nondrug therapies were not surveyed and are not discussed in this report.

MATERIALS AND METHODS

A brief questionnaire was distributed to all POG institutions via the newsletter and at the fall meeting in 1988 (Fig 1). The questionnaire focused on scoring the severity of nausea and vomiting associated with specific chemotherapeutic agents and current antiemetic practices at that institution.

The symptoms associated with specific chemotherapeutic agents were scored on a scale of 1 to 3, with 1 being least severe and 3 being most severe. The results were recorded in intervals of 0.5. A mean severity score was calculated for each agent for comparison purposes. Although these agents were often used in combination, an attempt was made to rate each agent individually. The frequency of antiemetic use and the drug or combination of drugs used to control nausea and vomiting was ascertained for mild, moderate, and severe chemotherapeutic agents. The responders were asked to specify modifications used, if any, for children younger than 5 years. In addition, the reasons for current antiemetic practices was evaluated. Responders were asked to rank two of a list of six possible reasons, including an "other" category. Differences between responses of physicians and nurses were tested with *t* tests or Wilcoxon rank sum tests where appropriate.

RESULTS

Current Usage

Responses were received from 76 individuals representing 46 POG institutions and affiliates. Seventy-one (93%) completed the entire questionnaire. Eighty-five percent (35 of 41) of member institutions and consortiums responded. Thirty-one institutions submitted a single response, 12 submitted responses from two individuals, and five submitted three or more responses. Differences in the responses were as common within as between institutions, although no formal statistical analysis was done.

Accepted for publication August 13, 1990.

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Reprints not available.

Please score each of the following agents, assigning a level of associated nausea and vomiting as follows:

- 1 = mild or no nausea and vomiting associated with the use of this agent.
 2 = moderate nausea and vomiting associated.
 3 = severe nausea and vomiting associated.
 X = no experience with this agent.

We realize many of these agents are used in combination, however, please attempt to rank each agent individually.

- | | |
|---|--|
| <input type="checkbox"/> Dactinomycin | <input type="checkbox"/> Doxorubicin |
| <input type="checkbox"/> L-Asparaginase | <input type="checkbox"/> Fluorouracil |
| <input type="checkbox"/> 5-Azaacytidine | <input type="checkbox"/> Hydroxyurea |
| <input type="checkbox"/> Carmustine | <input type="checkbox"/> Mercaptopurine orally |
| <input type="checkbox"/> Bleomycin | <input type="checkbox"/> Mercaptopurine intravenously |
| <input type="checkbox"/> Carboplatin | <input type="checkbox"/> Methotrexate 1gm/m ² |
| <input type="checkbox"/> Lomustine | <input type="checkbox"/> Methotrexate 1gm/m ² |
| <input type="checkbox"/> Iproplatin | <input type="checkbox"/> Nitrogen Mustard |
| <input type="checkbox"/> Cis-Platinum | <input type="checkbox"/> L-Phenylalanine Mustard |
| <input type="checkbox"/> Cyclophosphamide 10mg/kg | <input type="checkbox"/> Procarbazine |
| <input type="checkbox"/> Cyclophosphamide 10mg/kg | <input type="checkbox"/> Thioguanine |
| <input type="checkbox"/> Cytosine Arabinoside Std Dose | <input type="checkbox"/> Triple Intrathecal Therapy |
| <input type="checkbox"/> Cytosine Arabinoside High Dose | <input type="checkbox"/> Vinblastine |
| <input type="checkbox"/> Dacarbazine | <input type="checkbox"/> Vincristine |
| <input type="checkbox"/> Daunomycin | <input type="checkbox"/> Teniposide |
| | <input type="checkbox"/> Etoposide |

Please answer these questions for agents with each of the following scores for severity of associated nausea and vomiting.

1 = mild 2 = moderate 3 = severe

- In what percentage of patients do you use antiemetics when giving these agents?

- What drug or drug combination do you use in these settings? Please indicate the dose you would use for a 1 m² (30 kg) child.

 Do you modify these choices for children less than five years of age? If so, what agents are used? Please indicate the dose used for a 0.5 m² (10 kg) child.

- How effective are these antiemetics in these settings?
 1 = Highly effective
 2 = Moderately effective
 3 = Minimally effective

- Why have you chosen these antiemetics? Pick the two most important reasons from the following list and rank as:
 1 = Most important
 2 = Less important
 _____ Institutional policy
 _____ Past experience
 _____ Review of the literature
 _____ Parent or patient request
 _____ Advice from other oncologists or nurses
 _____ Other; please state.

Name (Optional) MD, RN, or other

Institution

Fig 1.—Questionnaire scoring severity of nausea and vomiting associated with specific chemotherapeutic agents and antiemetics.

The majority of responses (82%) were from physicians, with the remaining 18% coming from nurses or physician's assistants. There were no statistically significant differences between those two groups.

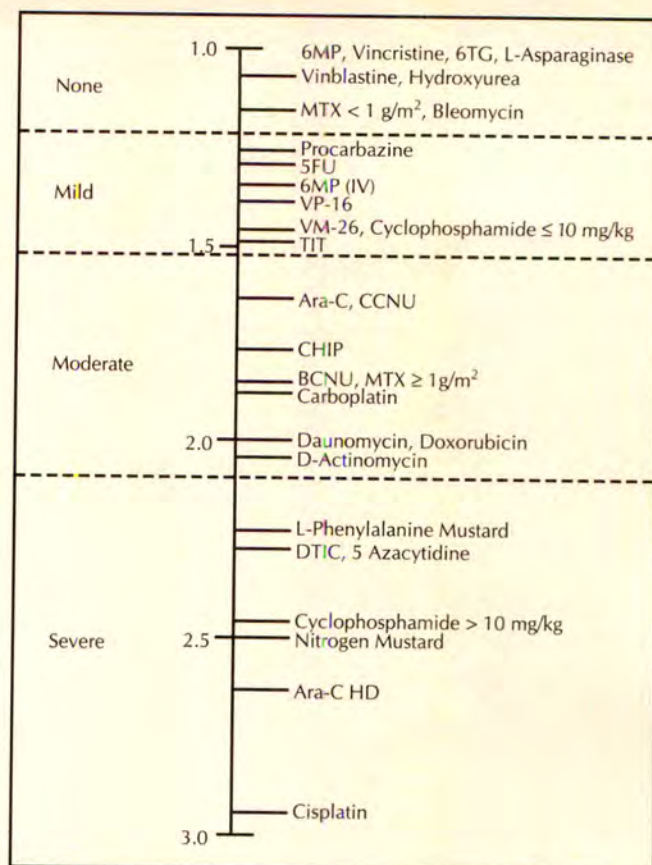


Fig 2.—Mean severity scores of nausea and vomiting associated with chemotherapeutic agents, according to the survey, indicated in rank order using a rating scale of 1 to 3, with 1 being least severe and 3 being most severe. 6MP indicates 6-mercaptopurine; 6TG, 6-thioguanine; MTX, methotrexate; IV, intravenous; 5FU, fluorouracil; VP-16, etoposide; VM-26, teniposide; Ara-C, cytarabine; CCNU, lomustine; CHIP, iproplatin; BCNU, carmustine; DTIC, dacarbazine; and TIT, triple intrathecal therapy of methotrexate, hydrocortisone, and cytarabine.

The mean severity rating for associated nausea and vomiting was calculated for each of 31 chemotherapeutic agents. The results are displayed in Fig 2 and are divided into four severity groups of approximately equal size.

The percentage of patients given antiemetics for chemotherapeutic agents with mild, moderate, or severe associated nausea and vomiting was determined. Antiemetics were used an average of 17% of the time with mild agents, 79% of the time with moderate agents, and 98% of the time with severe agents. The number of antiemetic drugs used also increased with the severity of expected nausea and vomiting. A median (mean) of 1 (1.4), 2 (2.0), and 3 (3.1) antiemetics were used per course for agents with mild, moderate, and severe nausea and vomiting, respectively. Several responders reported using as many as five antiemetics in combination to control symptoms associated with agents causing moderate or severe nausea and vomiting. Antihistamines and phenothiazines were the most commonly used antiemetics in children, followed closely by metoclopramide hydrochloride, steroids, and lorazepam (Fig 3). While antihistamines are often given to prevent extrapyramidal side effects of other agents, 14 responders (18%) used them alone as antiemetic agents, primarily for agents with mild associated symptoms. Diphenhydramine hydrochloride was the antihistamine used

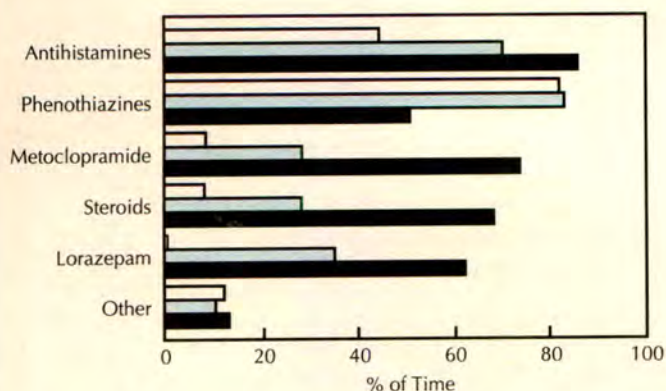


Fig 3.—Percentage of time each drug or drug class is used as an antiemetic for chemotherapeutic agents with mild (open bars), moderate (tinted bars), or severe (closed bars) associated nausea and vomiting. The amount shown is the percentage of time that the drug is given when antiemetics are used. The total percentage for each severity level is greater than 100% as multiple antiemetics are used per course of chemotherapy. Other drugs include tetrahydrocannabinol, phenobarbital, domperidone, trimethobenzamide, and scopolamine.

most often, accounting for 85% of all antihistamine usage. Hydroxyzine hydrochloride accounted for 13% and dimenhydrinate for 2% of antihistamines used. Chlorpromazine was the most commonly used phenothiazine, accounting for 51% of all usage. It was followed by promethazine hydrochloride, which accounted for 28% of phenothiazine usage. The tabulation below lists the generic and product names of phenothiazines used as antiemetics.

Generic Name	Product Name
Chlorpromazine	Thorazine, Largactil
Perphenazine	Trilafon
Prochlorperazine	Compazine
Promazine	Sparine
Promethazine	Phenergan, Mepergan
Thiethylperazine	Torecan

Other phenothiazines reported in the survey included thiethylperazine (8%), prochlorperazine (6%), perphenazine (5%), and promazine (2%). Dexamethasone was used 88% of the time that corticosteroids were given as antiemetics, and methylprednisolone accounted for the remaining 12%. The most common drug combinations were phenothiazine/antihistamine and metoclopramide/antihistamine, to which lorazepam and/or corticosteroids were added. Phenothiazines with or without antihistamines were preferred for chemotherapy with mild or moderate nausea and vomiting. Metoclopramide-based combinations were preferentially used for chemotherapy with severe associated nausea and vomiting. Metoclopramide/phenothiazine, or two different phenothiazine combinations, were occasionally used. All drugs were used primarily at recommended dosages, but there was a wide dosage range for many of the agents. For example, metoclopramide hydrochloride was used in doses ranging from 3 to 90 mg/m² (median, 30 mg/m²), lorazepam from 0.5 to 3 mg/m² (median, 1 mg/m²), and dexamethasone from 2 to 30 mg/m² (median, 10 mg/m²). Dosages used varied between responders; however, they did not vary with the severity of expected nausea and vomiting. Forty-

Table 1.—Reasons for Choice of Antiemetic Regimen			
Reasons	Ranked		Not Ranked
	Most Important	Second Most Important	
Experience	36	4	24
Literature review	4	13	11
Professional advice	2	9	10
Patient request	1	13	11
Other	1	1	2
Total	44	40	25*

*Multiple reasons listed account for total less than the sum of the individual reasons.

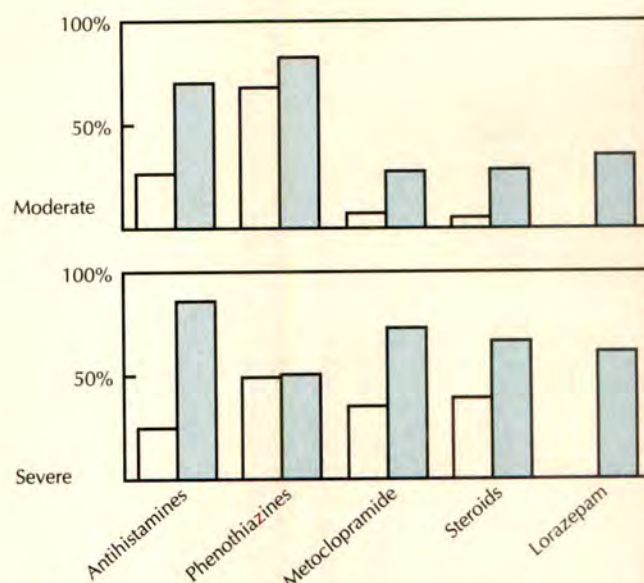


Fig 4.—Percentage of time each drug or drug class is used as an antiemetic for chemotherapeutic agents with moderate or severe associated nausea and vomiting, comparing 1984 (tinted bars) practice with 1988 (solid bars) practice. The total percentage for each severity level is greater than 100% as multiple antiemetics are used per course of chemotherapy.

two percent of responders made no change in choice or dose of antiemetics for children less than 5 years of age. Twenty-six percent decreased the dose per body surface area or weight to approximately 70% of the dose used for children older than 5 years. Sixteen percent of the responders reported withholding metoclopramide and lorazepam from children younger than 5 years.

Reasons for Use

The responders' clinical experience was the most important factor in the decision of which antiemetics to use. Thirty-six (82%) of the 44 responders who ranked their reasons for choosing a specific antiemetic regimen listed clinical experience as the most important reason (Table 1). Literature review, professional advice, and patient request were the next most frequently reported reasons for choosing particular antiemetics. Responders who reported several reasons without ranking them included experience as one of the reasons 96% of the time (Table 1), and literature review, professional advice, or patient request 40% of the time each.

Table 2.—Summary of Antiemetic Trials in Children Receiving Chemotherapy*

Source, y	Design†	No. of Patients	Conclusion
O'Meara and Mott, ²⁴ 1981	3	27	Domperidone safe and effective
Ise et al, ¹⁵ 1982	2	62	Methylprednisolone most, domperidone less, metoclopramide least effective
Khan et al, ²¹ 1983	2x	22	Dexamethasone/thorazine superior to thorazine alone
Zeltzer et al, ¹ 1984	2x	23	Phenothiazines worse than no therapy
Terrin et al, ¹⁶ 1984	3	8	Metoclopramide effective but high incidence of dystonic reactions
Allen et al, ¹⁷ 1985	3	45	Metoclopramide effective but extrapyramidal reactions, not all controlled with diphenhydramine
Ekert et al, ¹⁹ 1986	3	23	Dexamethasone/lorazepam/domperidone safe and effective
Howrie et al, ¹⁸ 1986	2x	11	Metoclopramide effective, high incidence of extrapyramidal reactions
Mehta et al, ¹³ 1986	1	20	Methylprednisolone as effective as chlorpromazine
Graham-Pole et al, ¹² 1986	1	50	Chlorpromazine superior to metoclopramide
Dalzell et al, ²³ 1986	1x	18	Nabilone superior to domperidone
Chan et al, ²² 1987	1x	30	Nabilone superior to prochlorperazine
van Hoff and Olszewski, ²⁰ 1988	2x	14	Lorazepam as effective as phenothiazine and/or methylprednisolone
Sumer et al, ¹⁰ 1988	1x	9	Dexamethasone superior to no therapy
Kobrinisky et al, ¹¹ 1988	1x	6	Naloxone worse than placebo
Marshall et al, ¹⁴ 1989	1x	26	Metoclopramide/benzotropine/dexamethasone/lorazepam superior to chlorpromazine

*Dosages discussed in the text.

† 1 represents randomized controlled trial; 2, controlled comparison trial, nonrandomized; 3, single course efficacy/safety trial; and x, crossover design.

Changes in Use

The use of antiemetics in children receiving chemotherapy has increased in recent years. The results from a survey conducted by a POG nursing committee in 1984 were compared with the results of this survey and are shown in Fig 4. Twenty-three institutions, many of which responded to this survey, participated in the 1984 descriptive survey. The 1984 survey solicited the antiemetics used for individual chemotherapeutic agents. The responses were similar for all agents except cisplatin. Therefore, the cisplatin responses from 1984 were compared with the severe agent responses in 1988, and the rest of the 1984 agents were compared with the 1988 moderate agents. Comparison of the two surveys revealed a general increase in the use of all agents, implying an increase in the number of antiemetic agents used per treatment course. Increased antihistamine use reflects its incorporation into antiemetic combinations. Metoclopramide, corticosteroids, and lorazepam use increased particularly between 1984 and 1988.

COMMENT

Nausea and vomiting related to chemotherapeutic agents are major problems in the treatment of cancer at all ages. In a prospective evaluation of chemotherapy-related nausea and vomiting, 92% of children who did not receive antiemetics had symptoms.² A more recent survey showed that 83% of children had nausea and 78% had vomiting after receiving chemotherapy without antiemetics.³ In both studies, the severity of symptoms varied substantially between patients and between successive courses of chemotherapy in the same patient. With repeated courses of chemotherapy, some children develop anticipatory nausea and vomiting that appears to have a different pathophysiologic mechanism than that induced

directly by chemotherapeutic agents.⁴ Anticipatory nausea has been noted in 28% to 36% of children; approximately 20% report anticipatory vomiting.^{3,4}

A rating scale of the emetogenic potency of various chemotherapeutic agents was developed for adults from a survey of medical oncology nurses,⁵ but similar data have not been previously reported for children. We present the results of an emetic potency survey in Fig 2, dividing the agents surveyed into groups with severe, moderate, mild, or no expected nausea and vomiting. Although this scoring system cannot be expected to predict each patient's response to particular chemotherapy, it can be used to help decide when to use antiemetics for children beginning chemotherapy. The emetogenicity of chemotherapeutic agents has been shown to strongly influence the severity of nausea and vomiting,^{4,6} although other non-drug factors such as age, sex, behavioral traits, and even child-rearing practices also play a role.^{3,4,6}

We also evaluated current antiemetic practices at 46 pediatric oncology centers. This survey was limited to pharmacologic antiemetic practices, although behavioral interventions may also be effective in children receiving chemotherapy.⁷⁻⁹ The results of this survey conflict somewhat with the limited available literature on antiemetic use in children. In August 1989, a total of 16 clinical trials evaluating antiemetic agents in children could be located by a computer search (Table 2). Seven of these studies were randomized controlled trials, and the others were sequential (n = 3) or single-course (n = 6) trials of agents or combinations of agents. Only three studies included a "no therapy"^{1,10} or placebo¹¹ arm and two of these concluded that the antiemetic studied exacerbated the nausea and vomiting.^{1,11}

Phenothiazines ranked among the most frequently used

antiemetics for children in this survey (Fig 3), yet the literature on their efficacy is inconclusive. Chlorpromazine (0.5 mg/kg every 3 hours) appeared more effective than a relatively low dosage of metoclopramide (0.5 mg/kg every 3 hours)¹² and equal to methylprednisolone¹³ in two reported randomized trials. The same drug was less effective than metoclopramide used at a higher dose (four 2-mg/kg doses) with dexamethasone, lorazepam, and benztropine in a randomized crossover trial.¹⁴ Prochlorperazine and chlorpromazine both appeared to increase the severity and duration of nausea and vomiting compared with no antiemetics in a sequential nonrandomized study.¹ However, the majority of those patients were given relatively low doses of prochlorperazine (12.5 or 25 mg) rectally. Antihistamines are commonly used as antiemetic agents, particularly in combination with phenothiazines or metoclopramide. There are no reported studies of their efficacy as antiemetics for children receiving chemotherapy, although physicians, as reported in this survey, use them as such, even as single agents.

Metoclopramide is commonly used as an antiemetic, and in this survey was the preferred antiemetic, in combination with other drugs, for chemotherapeutic agents with severe emetogenic potential (Fig 3). Metoclopramide's use in pediatric oncology centers increased substantially from 1984 to 1988 (Fig 4), in spite of the relative lack of support from published studies. Metoclopramide hydrochloride at low doses (0.5 mg/kg every 3 hours) was shown to be less effective than chlorpromazine¹² and less effective than either methylprednisolone or domperidone¹⁵ in comparative studies of children receiving chemotherapy. In addition, there were several reports that heavily emphasized metoclopramide's adverse side effects in children, particularly the extrapyramidal reactions.¹⁶⁻¹⁸ Subsequent experience has shown that these can usually be prevented by concomitant use of diphenhydramine. The single study demonstrating superiority of metoclopramide to chlorpromazine in children (when used with dexamethasone, lorazepam, and benztropine)¹⁴ was published after this survey was conducted. The use of lorazepam as an antiemetic also increased in spite of a paucity of literature supporting its use in children at the time of the survey. A single report mentioned its use with domperidone and dexamethasone in 1986.¹⁹ Since this survey, however, lorazepam's efficacy in combination¹⁴ and as a single agent at 0.05 mg/kg²⁰ has been reported.

Corticosteroids have been used increasingly and have received positive reports in the pediatric literature. Dexamethasone given at a dose of 1 mg/m² every 4 hours for 10 doses is the only agent that has been shown to be more effective than no antiemetics in a controlled trial.¹⁰ Dexamethasone (5 to 10 mg intravenously) also decreased nausea and vomiting when added to chlorpromazine.²¹ Methylprednisolone was more effective than metoclopramide or domperidone in one study,¹⁵ and at 4 mg/kg was equal in efficacy to chlorpromazine (0.5 mg/kg) in another.¹³

Two other agents deserve mention in a discussion of antiemetics for children receiving chemotherapy, although neither was licensed for use in the United States at the time of this survey. Nabilone (0.5 to 1.0 mg orally twice a day) has been shown to be more effective than prochlorperazine (5 to 10 mg orally twice a day)²² or dom-

peridone (5 to 10 mg orally twice a day)²³ in randomized crossover trials. Domperidone was effective both as a single agent²⁴ and in combination with dexamethasone and lorazepam,¹⁹ although it was not as effective as methylprednisolone¹⁵ or nabilone²³ in comparative trials.

Pediatric oncologists are using an increasing number of antiemetics, often in combinations that have not been studied in children. This may incur risks, as children, particularly young children, may experience unique or more severe side effects compared with adults.^{16-18,20,25} This study suggests that the choice of agents is based on experience, not on prospective controlled trials, resulting in a lack of consensus regarding appropriate antiemetic therapy for children. There are many obstacles to an organized study of antiemetics for children, the principal one being the number of available subjects. The infrequency of childhood cancer and the wide variety of types of cancer and treatment regimens make the assembly of a sizable homogeneous group difficult. Individual variation in the susceptibility to nausea and vomiting, as well as the frequent lack of complete response to pharmacologic agents in current use, are additional factors that make antiemetic studies difficult. Nonetheless, pediatric oncologists should put a priority on participating in randomized controlled trials of antiemetics to improve our present understanding of and therapy for chemotherapy-related nausea and vomiting in children. Additional studies of the four-drug regimen now in routine use (metoclopramide, diphenhydramine, dexamethasone, and lorazepam) to determine which components are the most effective would be particularly helpful. The optimal combination could then be compared with the new serotonin antagonists that are now being used in clinical trials.²⁶ In addition, behavioral techniques should be compared with the available pharmacologic agents. Finally, pediatric oncologists should depend more heavily on clinical trials when choosing antiemetics to quickly implement the most effective and least toxic regimens.

This study was supported in part by grant RR-125 (General Clinical Research Center) from the National Institutes of Health; and by a Clinical Oncology Career Development Award from the American Cancer Society (Dr van Hoff) (CA-205549, CA-41188, CA-33603, CA-30969). We acknowledge the members and administrative office of the Pediatric Oncology Group, St Louis, Mo, for their assistance. The following is a list of POGs participating in this study, with the principal investigators and grant number in parentheses: Alberta Pediatric Oncology Consortium, Edmonton (John Akabutu, MD); Baylor College of Medicine, Houston, Tex (Donald Fernbach, MD; CA-03161); Bowman Gray School of Medicine, Winston-Salem, NC (Richard Patterson, MD; CA-15525); Boston (Mass) Floating Hospital (Molly Schwenn, MD); Children's Hospital of Michigan, Detroit (Y. Ravindranath, MD; CA-29691); City of Hope, Duarte, Calif (Patricia Konrad, MD; CA-32278); Dana-Farber Cancer Institute, Boston, Mass (Howard Weinstein, MD; CA-41573); Duke University, Durham, NC (John Falletta, MD; CA-15525); Emory University School of Medicine, Atlanta, Ga (Abdel Ragab, MD; CA-20549); Johns Hopkins University, Baltimore, Md (Brigid Leventhal, MD; CA-28476); McGill University, Montreal, Quebec, Children's Hospital (Michael Whitehead, MD; CA-33587); Medical College of Virginia, Richmond (Harold Maurer, MD; CA-28530); Medical University of South Carolina, Charleston (Biemann Othersen, MD); Midwest Children's Cancer Center, Milwaukee, Wis (Bruce Camitta, MD; CA-32053); New England Pediatric Oncology Consortium, Providence, RI (Edwin Forman, MD; CA-29293); Mount Sinai School of Medicine, New York, NY (Jeffery Lipton, MD, PhD); Oklahoma University, Oklahoma City (R. Nitschke, MD; CA-11233); Roswell Park Memorial Institute, Buffalo, NY (Martin Brecher, MD; CA-28383); St Christopher's Hospital for Children, Philadelphia, Pa (Robert Wimmer, MD); St Jude Children's

Research Hospital, Memphis, Tenn (H-C Pui, MD; CA-31566); Stanford University, Palo Alto, Calif (Michael Link, MD; CA-33603); SUNY Health Science Center, Syracuse, NY (Ronald Dubowy, MD; CA-41721); Swiss Pediatric Oncology Group, Bern, Switzerland (Hans Wagner, MD); University of California, San Diego (Faith Kung, MD; CA-28439); University of Florida, Gainesville (Samuel Gross, MD; CA-29281); University of Kansas, Kansas City (Tribhawan Vats, MD; CA-28841); University of Miami (Fla) (Stuart Toledano, MD; CA-41082); University of Mississippi, Jackson (Jeanette Pullen, MD; CA-15989); University of Texas M. D. Anderson Center, Houston (Donald Pinkel, MD; CA-03713); University of Virginia, Richmond (Beverly Raney, MD); Washington University, St Louis, Mo (Vita Land, MD; CA-05587); Yale University School of Medicine, New Haven, Conn (Peter Beardsley, MD, PhD); Florida Community Clinical Oncology Program (James Talbert, MD; CA-35157).

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Injuries and Poisonings in Out-of-Home Child Care and Home Care

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● As part of a national telephone survey regarding health events associated with out-of-home child care, data regarding poisonings and injuries were collected. Of 171 reported poisonings, none occurred during out-of-home child care. The rate of injury during out-of-home child care was 1.69 per 100 000 child-hours compared with 2.66 for home care. Overall injury rates were slightly higher for children who attended out-of-home child care than for those who do not. This occurred because children who attended out-of-home child care had a higher injury rate during home care than did the children who did not attend out-of-home child care at all. Although out-of-home child care may carry an increased risk of infectious disease relative to home care, it does not appear to carry an increased risk of injury and, in fact, may confer a lower risk.

(AJDC. 1991;145:779-781)

Recent studies have raised concern that out-of-home child care (OHC) may expose children to an excessive risk of injury.¹⁻⁸ In the first study to document that OHC was as safe, if not safer, than home care (HC), Rivara and coworkers⁹ calculated a medically attended injury rate of 2.50 per 100 000 child-hours for OHC compared with 4.88 for HC. As part of a national telephone survey conducted in 1987 about health events associated with OHC, we report herein on data we obtained about injuries and poisonings.

METHODS

The nationwide random-digit dialing clustered-sample telephone survey has been described in detail elsewhere.¹⁰ Briefly, to compare rates of health events between OHC and HC, the study was designed to enroll at least 262 children in OHC and 262 children with no OHC in each of three age groups: 6 weeks to 17 months, 18 to 35 months, and 36 to 59 months. These age groups were chosen, in part, to facilitate separate data analysis for diapered and nondiapered children for the study of infectious disease-related issues.

Accepted for publication September 11, 1990.

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For the present study, OHC was defined as spending 10 hours or more per week in any care setting outside the child's home for at least a 4-week period during the year preceding the interview. Part-year OHC was defined as attending OHC for less than 12 months during the preceding year. Home care was defined as the time not spent in OHC. A child with no exposure to OHC was classified as "HC only."

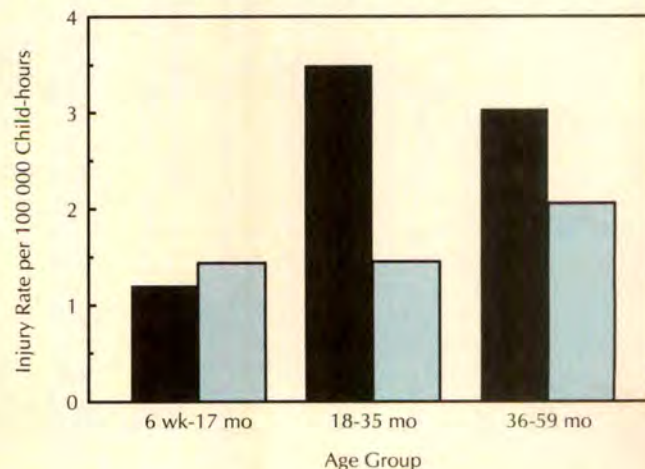
Of a total of 35 000 households called, 28 500 (81%) participated, and 2853 households had children under 5 years of age. Based on enrollment needs in each age and OHC-exposure group, detailed information regarding child care and health events was collected from 1775 households that included 2250 children under 5 years of age.

An adult respondent was asked the following questions: "During the past year, have any of your children had an accident or injury that required a visit to a doctor or hospital?" "During the past year, has there been any incident where you had to contact a doctor or poison control center about a possible poisoning of one of your children?" Information was collected regarding the nature and place of occurrence of each injury or poisoning event, but not the date or time.

Dates of enrollment and average hours per week in each OHC setting were used to calculate site-specific OHC hours at risk. Because 98% of all childhood injuries occur between 7 AM and 10 PM,¹¹ we assumed that a child was at risk of injury 15 hours per day (105 hours per week). Home care hours at risk were then calculated as 105 hours minus the weekly hours spent in OHC.

Overall rates per 100 child-years and site-specific rates per

Injury rate per 100 000 child-hours by age group and location. Black bars indicate home care; shaded bars, out-of-home care.



Rate of Injury per 100 000 Child-hours by Age Group and OHC Exposure*

OHC Exposure	Injury Rate per 100 000 Child-hours							
	6 wk-17mo		18-35 mo		36-59 mo		Total	
	HC	OHC	HC	OHC	HC	OHC	HC	OHC
Any OHC	0.89	1.43	4.63	1.42	3.59	2.04	3.40†	1.69‡
HC only	1.28	...	3.00	...	2.63	...	2.31	...
Total§	1.20	1.43	3.50	1.42	3.02	2.04	2.66	1.69

*OHC indicates out-of-home care; HC, home care.

†The rate for full-year OHC = 4.35; part-year OHC = 2.61.

‡The OHC rate for full-year OHC = 1.47; part-year OHC = 2.16.

§Any OHC plus HC only.

100 000 child-hours for both injuries and poisonings were calculated for the three age groups (6 weeks to 17 months, 18 to 35 months, and 36 to 59 months) and for three OHC-exposure groups (HC only, part-year OHC, and full-year OHC). To ensure the independence of all observations within an age group, only one child, the youngest, was selected from any one household. Rates were adjusted for the probability of selection imposed by the sampling plan. Rate ratios were adjusted for age, family income, and region; 95% confidence intervals were calculated with the method of Breslow and Day.¹² Statistical comparisons were performed only within age groups.

For descriptive purposes, all eligible children in the household were used in the following analyses: injury rate by type of OHC, type of injuries during OHC and HC, and aggregate injury rates for all age groups combined. Because of the nonindependence of these observations, no statistical comparisons were made.

RESULTS Injuries

The overall injury rate was 15.2 per 100 child-years. For those aged 6 weeks to 17 months, the overall rate was 7.3 per 100 child-years compared with 18.7 for those aged 18 to 35 months and 17.3 for those aged 36 to 59 months. For children with HC only, the injury rate was 13.6 per 100 child-years compared with 17.8 for children with any exposure to OHC (children in full-year OHC, 20.2; children in part-year OHC, 15.4). The adjusted injury rate ratios for any OHC vs HC only were 0.77, 1.32, and 1.23 for children aged 6 weeks to 17 months, 18 to 35 months, and 36 to 59 months, respectively. The 95% confidence interval for all of these ratios included one.

The injury rate for OHC was 1.69 per 100 000 child-hours compared with 2.66 for HC. The effect of OHC on injury rate differed with age (Figure); only the two older age groups showed a decreased injury rate during OHC. The adjusted injury rate ratios for OHC vs HC were 1.22, 0.40, and 0.65 for children ages 6 weeks to 17 months, 18 to 35 months, and 36 to 59 months, respectively. This risk differed significantly from one for children aged 18 to 35 months ($P = .02$).

Children aged 18 months through 59 months who had any exposure to OHC had (1) higher rates of injury during HC compared with OHC and (2) a higher injury rate during HC than in comparably aged children with HC only (Table). The opposite results were found in the children aged 6 weeks to 17 months.

By OHC type, the injury rate was 3.95 per 100 000 child-hours in day-care homes, 2.18 in institutional day-care settings, and 0.74 in other OHC settings.

Two of the injuries (a fracture and a head injury), neither of which occurred during OHC, resulted in overnight hospitalization. Of 280 injuries reported as having occurred

during HC, 76.1% occurred in the child's own home or yard. Cuts and bruises were the most common injuries (40.4%) during HC, followed by head injuries (16.8%), eye injuries (7.9%), and fractures (5.7%). Of 24 injuries occurring during OHC, head injuries were the most common (37.5%), followed by cuts and bruises (25.0%) and fractures (4.2%). Six burns occurred during HC compared with none during OHC.

Poisonings

Of 171 poisonings, none occurred during OHC. The poisoning agents were medicines (50 [29.2%]), chemicals (32 [18.7%]), plants (30 [17.5%]), cleaning agents (25 [14.6%]), and other agents (34 [19.9%]). The agent differed with the age of the child; for those aged 6 weeks to 17 months, plants were the leading cause (40.0%); for those aged 18 to 35 months, chemicals (25.6%); and for those aged 36 to 59 months, medicines (45.9%). The pattern of poisoning rates was similar to that for injuries. For each age group, the HC poisoning rate for those who attended OHC was higher than that for children with HC only.

COMMENT

Our results suggest that the rate of injury and poisoning is lower during OHC than HC. However, the child who attends OHC has a higher rate of injury during HC than does the child who does not attend OHC at all. Indeed, the overall injury rate was slightly higher for children who attended OHC than for those who did not.

Injury rates during OHC and HC are not directly comparable, because the times of day and days of the week were distributed differently between the two. For children who attend OHC, HC hours are mainly during evenings and weekends; OHC hours are mainly daytime weekday hours. For the HC only group, HC hours reflect a mixture of weekday, weekend, and evening hours. Because childhood injuries are more likely to occur during daytime than evening hours and are more likely to occur on weekdays than weekends,¹¹ adjusting for the differing time periods would presumably further decrease the OHC rate relative to the HC rate.

Ascertainment and recall problems may have affected our results. Parents may not have been as aware of injuries and poisonings occurring during OHC as during HC. If an OHC provider's call to a poison control center determined that an exposure did not warrant treatment, the parents may not have been told about the event, and we may therefore have underestimated OHC poisonings. However, because reported injuries were medically attended ones, either the OHC provider took the child for medical care without telling the parents or parents did not

recall injuries that occur during OHC as well as those that occur during HC. We think both possibilities are unlikely. For those in the full-year OHC group, the HC injury rate was markedly higher (4.35) than the OHC rate (1.47); for those in the part-year OHC group, the HC rate (2.61) was more similar to the OHC rate (2.16). Because the midpoint of OHC exposure in the year preceding the study was further from the interview date in the full-year OHC group than in the part-year OHC group, injuries that occurred during OHC presumably occurred further from the interview date for the full-year OHC group. Thus, recall problems about location may have been greater for the full-year OHC group.

Beyond recall problems, differences in supervision, behavior, and environment may explain why children with any OHC have higher injury rates during HC. After work, parents of children exposed to OHC may have to spend time preparing meals or otherwise managing the home instead of supervising the child. Parents of children in full-time HC may be able to accomplish such tasks while the child naps. On release from the structured, controlled OHC environment, children may exhibit more reckless behavior; the child in full-time HC may exhibit more constant behavior. Some parents may place hard-to-manage children in OHC. The HC environments of children in OHC may not be as completely "child-proofed" as those of children in full-time HC. Further research should verify whether the rate differences remain, explore potential explanations, and define the time and circumstances of injuries in HC.

Based on reports from child-care center directors, Sacks and coworkers⁵ calculated a medically attended injury rate of 1.56 per 100 000 child-hours for children under 5 years of age in child-care centers. This figure is 28% lower than our estimate (2.18) for injuries in child-care centers. The rate estimates of Rivara et al,⁹ on the other hand, are 83% higher than ours for HC (4.88 vs 2.66) and 48% higher than ours for OHC (2.50 vs 1.69). That our results are intermediate and that our findings confirm those of Rivara et al suggest that our estimates are reasonable and not

grossly distorted from biases.

Despite the limitations of our study, we believe that our analysis sheds light on the relative safety of OHC and HC. The data on poisonings overwhelmingly favor OHC as being safer. Although OHC, compared with HC, may carry an increased risk of infectious disease,¹³ it does not appear to carry an increased risk of injury and, in fact, may confer a lower risk of injury.

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A Longitudinal Study of Birth Weight and Being Overweight in Late Adolescence

Daniel S. Seidman, MD; Arie Laor, MD; Rena Gale, MD; David K. Stevenson, MD; Yehuda L. Danon, MD

● A total of 33 413 infants born in Jerusalem between 1964 and 1971 were followed up at 17 years of age by matching computerized database files. A logistic regression model was used to estimate the odds ratios for being overweight at 17 years of age for 500-g birth weight categories from less than 2500 g to 4500 g or greater. Information on the ethnic origin, paternal education, birth order, maternal age, and area of residence at birth was available, and these factors were used as possible confounders. The adjusted odds ratios for being overweight (≥ 90 th percentile; body mass index > 24.6 kg/m²) and severely overweight (≥ 97 th percentile; body mass index > 27.8 kg/m²) at 17 years of age was elevated for the three birth weight categories above the normal reference category of 3000 to 3499 g, with an estimate of 2.16 and 2.30 for male subjects with a birth weight greater than 4500 g and 2.95 and 4.39 for female subjects. The data suggest that higher birth weights correlate strongly with being overweight in late adolescence independently of other factors considered. However, the predictive power of this association is poor.

(AJDC. 1991;145:782-785)

Obesity is a well-established health hazard.¹ As the long-term results of treatment are discouraging, more attention is being directed toward prevention and the study of groups at particular risk. The possible association of being overweight during infancy and adult obesity is important, because it may contribute to our understanding of genetic, metabolic, and environmental predisposing factors.² The relationship of adult obesity with weight at 1 year of age or older has been recognized.^{3,4} However, a predictive pattern for adult obesity is still not proved regarding birth weight.^{2,5}

The discrepancies found between results of previous studies that examined the link between birth weight and being overweight as an adult may be due to short follow-up periods,^{6,7} recall bias,⁸ and limited sample

size.^{9,10} We examined the risk for being overweight at 17 years of age by birth weight in a sample of 33 413 subjects born in Jerusalem, Israel.

SUBJECTS AND METHODS

The study population consisted of 33 413 subjects born in Jerusalem between 1964 and 1971. Birth weights, recorded at the time of delivery, were obtained from the computerized files of the Jerusalem Perinatal Study.^{11,12} The Jerusalem Perinatal Study was a population-based study that included all of the deliveries at the three major obstetric wards in Jerusalem during the years 1964 through 1976. Body weight and height measurements at 17 years of age, as well as detailed demographic data, were available from the Israel Defence Forces draft medical examination computerized records.¹³ Standing body height was measured without shoes to the nearest 1 cm, and nude body weight was determined to the nearest 100 g. The data for each individual were matched with use of a seven-digit identification number. The completeness of the match was confirmed by comparing sex and maternal identity number. Females consisted of only 38.3% of our study population, because girls who declare themselves to be orthodox religious are exempt from compulsory service.¹³ The results are thus presented separately for male and female subjects. Only a negligible minority of patients hospitalized for severe chronic and psychiatric diseases and long-term prisoners were not examined and consequently were not included in our data.¹³

A multiple logistic regression analysis with the Logist procedure of SAS software¹⁴ was performed by a stepwise method to adjust for the effect of the studied independent variables. Separate models were estimated for male and female subjects. Being overweight, and being severely overweight, were used as dependent variables. Overweight was defined as a body mass index (body weight in kilograms/[height in meters]²) equal to or greater than the 90th percentile of 17-year-old male and female adolescents examined at the Israel Defence Forces draft board (> 24.6 kg/m² for both male and female subjects). Severely overweight was defined as a body mass index equal to or greater than that at the 97th percentile of the same population (> 27.8 kg/m² for male subjects and > 27.7 kg/m² for female subjects). The independent variables used in the analysis were birth weight (500-g categories from < 2500 g to ≥ 4500 g to provide a clinically relevant estimate of the associated risk), ethnic origin (defined according to paternal country of birth), area of residence (classified by municipal tax level areas¹²), maternal age (as a continuous variable), paternal educational attainment level, and birth order (categorized to avoid dubious assumptions about linearity). All variables that were significant at the .05 level were added to a model that contained the birth weight variable.

The results of the logistic regressions are presented as adjusted odds ratios and their 95% confidence intervals (ie, $e^{b \pm 1.96s}$, where b is the logistic regression coefficient and s is its estimated standard error). The estimates presented are based on the exclusion of cases with missing values (1.9%).

Accepted for publication January 29, 1991.

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Table 1.—Distribution of Population Characteristics and Prevalence of Overweight and Severely Overweight at 17 Years of Age Among 33 547 Subjects Born in Jerusalem, Israel, Between 1964 and 1971*

Population Characteristics	Male (n=20 747)			Female (n=12 666)		
	% of Population	% Overweight	% Severely Overweight	% of Population	% Overweight	% Severely Overweight
All	100.0	10.2	3.0	100.0	10.1	3.1
Ethnic origin†						
Israel	14.9	12.4‡	4.2‡	13.1	9.4	3.5§
Asia	33.3	10.2	2.6	34.7	10.5	3.0
Africa	23.5	7.9	2.2	23.3	11.1	3.9
West	28.3	12.4	3.6	28.9	9.3	2.3
Paternal educational attainment, y of schooling						
<8	37.2	10.4	2.8§	36.8	11.6‡	4.0§
8-12	38.7	10.8	3.5	37.9	9.8	2.7
>12	24.1	9.5	2.8	25.3	8.1	2.1
Birth order						
1	28.2	10.6	3.3	32.7	10.0	3.3
2	23.3	9.5	2.7	26.6	9.6	2.9
3-4	26.8	10.4	3.1	26.7	10.0	2.7
≥5	21.7	10.4	3.0	14.0	11.5	3.3
Area of residence, municipal tax level						
High	26.3	10.6	3.3	26.0	8.7§	3.0
Medium	33.8	10.5	3.2	34.3	10.5	3.0
Low	39.9	9.7	2.8	39.7	10.8	3.1
Birth weight, g						
<2500	4.7	9.2‡	2.9‡	5.3	8.2§	2.6‡
2500-2999	16.3	7.9	2.0	22.8	8.4	2.6
3000-3499	41.2	9.4	2.8	45.2	9.6	2.8
3500-3999	28.8	11.3	3.4	21.7	12.5	3.8
4000-4499	7.8	15.1	4.9	4.5	13.2	4.9
≥4500	1.2	18.2	6.0	0.5	23.3	10.0

*Overweight was defined as body mass index greater than 24.6 kg/m², and severely overweight was defined as body mass index greater than 27.8 kg/m².

†Ethnic origin was defined by paternal country of birth.

‡χ² test comparing overweight and severely overweight groups with the total population, *P*<.001.

§χ² test comparing overweight and severely overweight groups with the total population, *P*<.01.

RESULTS

Table 1 gives the percentage of overweight and severely overweight 17-year-old subjects according to the independent variables included in the analyses. The table also indicates that ethnic origin, paternal educational attainment level, and area of residence are associated with significantly different rates of overweight and severely overweight subjects. A strong and apparently linear link is observed between birth weights of more than 3000 g and the prevalence of being both overweight and severely overweight, regardless of sex.

The association of the birth weight groups with being overweight was analyzed with the use of multiple logistic regression to control for the effects of confounding variables. All of the variables in Table 1 were analyzed. The final model for overweight reached by the stepwise procedure included the birth weight variable and four confounders (paternal education, area of residence, ethnic origin, and birth order) for male subjects and only one confounder (paternal education) for female subjects

(Table 2). The final regression model for severely overweight eliminated all independent variables, except birth weight and two confounders (paternal education and ethnic origin for male subjects and paternal education and maternal age for female subjects) (Table 3). Logistic analysis of these data confirmed the significant (*P*<.001) positive association between birth weights of 3000 g or more and being overweight and severely overweight at 17 years of age (Tables 2 and 3).

COMMENT

Higher birth weight was found to be a risk factor for obesity in late adolescence. To our knowledge, ours is the first study of its kind based on a large data base of recorded birth weights and a long follow-up period of 17 years. The results may thus shed light on the conflicting data reported in previously published studies. Some investigators have found a clear-cut relationship between birth weight and obesity in later childhood^{6,15,16}; others have found no cor-

Table 2.—Adjusted Odds Ratios for Being Overweight at 17 Years of Age Among 33 547 Subjects Born in Jerusalem, Israel, Between 1964 and 1971*

Birth weight, g	Adjusted Odds Ratios (95% Confidence Interval)	
	Males (n=20 324)	Females (n=12 672)
<2500	1.04 (0.79-1.28)	0.83 (0.62-1.10)
2500-2999	0.81 (0.69-0.94)	0.87 (0.74-1.02)
3000-3499†	1.00	1.00
3500-3999	1.25 (1.12-1.39)	1.34 (1.16-1.54)
4000-4499	1.72 (1.74-2.02)	1.35 (1.03-1.77)
≥4500	2.16 (1.54-3.04)	2.95 (1.59-5.49)

*Overweight was defined as body mass index greater than 24.6 kg/m².

†Reference group.

Table 3.—Adjusted Odds Ratios for Being Severely Overweight at 17 Years of Age Among 33 547 Subjects Born in Jerusalem, Israel, Between 1964 and 1971*

Birth Weight, g	Adjusted Odds Ratios(95% Confidence Interval)	
	Males (n=20 324)	Females (n=12 672)
<2500	1.09 (0.72-1.64)	0.93 (0.56-1.54)
2500-2999	0.74 (0.56-0.98)	0.94 (0.71-1.25)
3000-3499†	1.00	1.00
3500-3999	1.26 (1.04-1.54)	1.41 (1.09-1.82)
4000-4499	1.83 (1.40-2.40)	1.79 (1.36-2.76)
≥4500	2.30 (1.33-3.95)	4.39 (1.82-10.58)

*Severely overweight was defined as body mass index greater than 27.8 kg/m².

†Reference group.

relation between high birth weight and subsequent obesity.^{5,9,10} A high correlation between birth weight and adult body mass is usually attributed to a genetic effect. The variance in birth weight has been shown to be largely determined by fetal genes.¹⁷ Obesity has similarly been found to be strongly dependent on genetic factors.¹⁸ Common mechanisms affecting both birth weight and adult obesity have therefore been suggested, including an in-born error in adipose tissue regulation and inherited abnormal mechanisms controlling food intake and systemic energy expenditure.¹⁹ None of these hypotheses has been substantiated thus far, and the influence of genetic factors on the development and structure of adipose tissue in humans is poorly understood.²⁰

Ethnic and environmental factors may also have an important influence on adult body weight. Medical insurance is widely available in Israel, and almost the entire population (95%) is insured in one of the nation's sick funds.²¹ Virtually all of the mothers thus receive prenatal care as well as perinatal and child care at one of the Mother and Child Health Centers.^{12,21} The effect of birth weight was adjusted in our study for the possible confounding effects of ethnic origin^{22,23} and socioeconomic status (determined according to paternal education attainment level and area of residence).²⁴ However, it was not possible to control for the influence of parental body mass. We have recently shown that birth weight is significantly ($P<.001$) related in the Jerusalem population to maternal prepregnant body mass.²⁵

Overweight mothers may be more likely to overfeed their infants.²⁶ Such a trend toward infantile overnutrition may predispose to obesity in later childhood and adulthood.²⁷ This suggestion is consistent with the possible

causative role of adipose cell hyperplasia largely determined in early life.^{20,28} Mossberg¹⁵ has recently shown that the degree of obesity in parents is among the most important factors for weight level in adulthood.

Eid⁷ suggested that infants with a lower birth weight may gain weight more rapidly than those with a higher birth weight and may therefore be at a greater risk of subsequent obesity. Binkin et al⁶ have recently shown that although infants with low birth weight exhibit proportionately greater weight gain in the first year of life, they tend to remain shorter and lighter in early childhood compared with children with higher birth weights. We found the body mass at 17 years of age of low-birth-weight (<2500 g) infants not to differ from that of the reference group (birth weight 3000 to 3499 g). However, the possibility that below-average birth weight (2500 to 2999 g) may offer some long-term benefit in terms of reduced obesity in adulthood could be suggested. It should be remembered that we could not fully assess the effect of intrauterine growth retardation on future growth, as gestational age was unavailable.

Our results may increase our ability to identify those children who are more prone to becoming overweight adults and to more clearly define risk groups. However, despite the observation that in contrast to the normal-birth-weight group a greater proportion of the overweight subjects had higher birth weights, the predictive power of this association is poor. In fact, most of the overweight adults in our study had normal birth weights. The search for predictive markers for adult obesity continues as data linking high body mass index in early adulthood with mortality are accumulating.^{29,30} Van Itallie³⁰ has suggested that being overweight during early adulthood is even more dangerous than a similar degree of being overweight in later adult life. Nevertheless, despite the increased risk for obese children of being obese as adults,³¹ a weight-reducing diet very early in life could be harmful to the child's growth and development.³² Our results imply that although being overweight at birth increases the risk of being overweight in late adolescence, it has little predictive power and may reflect body build more than adiposity.

This work was supported in part by the Doron Foundation, Tel-Aviv, Israel.

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Guidelines for Auditing Pediatric Blood Transfusion Practices

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● Although transfusion of blood products is an essential and potentially life-saving measure, not all blood transfusions are beneficial to patients. The associated risks, particularly transfusion-transmitted viral illnesses, such as hepatitis and acquired immunodeficiency syndrome, require that careful consideration be given before a decision is made to transfuse any blood product. Many institutions have established a local committee to monitor transfusion practices and audit such practices regularly. To assist in this task, the Pediatric Hemotherapy Committee of the American Association of Blood Banks has developed guidelines for the conduct of pediatric blood transfusion audits. These guidelines, summarized herein, cover transfusion of red blood cells, platelets, white blood cells, fresh-frozen plasma, albumin, and clotting concentrates. The use of cytomegalovirus low-risk and irradiated blood products is also discussed. Throughout the report, special attention is given to the transfusion needs of newborn infants.

(AJDC. 1991;145:787-796)

Transfusions are essential in many clinical situations. Although current blood-banking practices have reduced the risks of transfusion, transmission of infections, particularly hepatitis C, continues to be of concern.¹ Fortunately, transmission of the human immunodeficiency virus type 1, the cause of the acquired immunodeficiency syndrome, is now very rare.² Noninfectious risks include immune-mediated hemolytic and allergic reactions, graft-vs-host disease, and iron overload. Because of these risks, it is recommended that informed consent be obtained and documented for all nonemergency blood transfusions,³ and decisions to transfuse blood products should reflect

consideration of the risk/benefit ratio. Auditing of transfusion practices is one method of addressing this issue.

Transfusion practice guidelines, developed to assist in conducting audits, simply provide a list of acceptable clinical circumstances in which transfusions may be given without need for additional justification. However, they should not serve as absolute indications for transfusion therapy. On the one hand, not all patients eligible to receive a transfusion according to the guidelines would actually benefit from one; on the other hand, some transfusions judged inappropriate by guidelines may be justified because of special clinical circumstances. Such transfusions require explanation, a task that usually involves review of the patient's medical records or a request for additional information from the patient's physician by the local transfusion committee.

Given this background, the Pediatric Hemotherapy Committee of the American Association of Blood Banks has developed guidelines for auditing pediatric transfusions (Tables 1 through 7). These criteria apply to infants and children younger than 18 years, except when otherwise stated; statements in the tables that are underlined require additional definition by each local transfusion committee. This format was selected to permit flexibility and to ensure consistency with local standards of practice.

TRANSFUSION OF WHOLE BLOOD OR RECONSTITUTED WHOLE BLOOD

Reconstituted whole blood (red blood cells [RBCs] reconstituted with fresh-frozen plasma [FFP]) or whole blood (≤ 5 days old) may be given without the need for further justification in the setting of massive transfusions (Table 1). Acute blood loss (in the absence of documented coagulation abnormalities) should be treated with whole blood or reconstituted whole blood only when replacement of losses with

Table 1.—Criteria for Transfusion of Whole Blood or Reconstituted Whole Blood

1. Massive transfusion or acute blood loss (>1 blood volume* in < 24 h)
2. Exchange transfusion
3. Cardiovascular bypass surgery
4. Extracorporeal membrane oxygenation

*Estimated as 70 mL/kg of body weight.

Accepted for publication January 10, 1991.

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This report expresses the opinions of the authors and does not represent official policy of the American Association of Blood Banks.

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Table 2.—Criteria for Transfusion of Red Blood Cells***Neonates younger than 4 months**

1. Venous hemoglobin level <130 g/L in neonates <24 h old
2. Hemoglobin level <130 g/L and severe pulmonary disease, cyanotic heart disease, or heart failure
3. Acute blood loss $\geq 10\%$ of total blood volume
4. Phlebotomy losses $\geq 5\%$ -10% of the total blood volume
5. Hemoglobin level <80 g/L in stable newborn infants with clinical manifestations of anemia

Patients 4 months of age

1. Significant preoperative anemia; intraoperative blood loss $\geq 15\%$ of total blood volume; postoperative hemoglobin level <80 g/L, and symptoms or signs of anemia
2. Acute blood loss with hypovolemia unresponsive to crystalloid or colloid
3. Hemoglobin level <130 g/L in patients with severe pulmonary disease requiring assisted ventilation
4. Chronic congenital or acquired anemia without an expected satisfactory response to medical therapy and a hemoglobin level <80 g/L, or a hemoglobin level <100 g/L with symptoms and/or signs of anemia
5. Chronic transfusions to suppress endogenous hemoglobin production in selected patients with sickle-cell or thalassemia syndromes
6. Induction of immune tolerance before renal transplantation

*Statements that are underlined require additional definition by each local transfusion committee.

RBCs and crystalloid or colloid would dilute coagulation factors to levels insufficient to ensure hemostasis. In adults, such dilution is thought to occur once acute blood loss exceeds one blood volume^{4,5}; in the neonate and young infant, the comparable value, although unknown, is presumed to be similar. However, levels of several coagulation factors are lower in neonates,^{6,7} and it is possible that very young infants may require coagulation factor replacement after smaller losses.

TRANSFUSION OF RBCs

Although RBCs are the most commonly transfused blood component, the pediatric literature (particularly outside the neonatal period) is remarkable for the paucity of carefully designed studies investigating the benefits and/or risks associated with this therapy. The guidelines that follow are therefore based, in many instances, on expert opinion and common practice rather than on the results of scientific studies.

Neonates and Infants Younger Than 4 Months

Guidelines for RBC transfusions in neonates are presented in Table 2 (hereafter, the term *neonates* refers to both neonates and infants younger than 4 months). Mean hemoglobin values (± 2 SDs) in normal term and preterm (32 weeks' gestation) newborns at 24 hours of life are 193 ± 22 g/L and 185 ± 20 g/L, respectively.⁸ A venous hemoglobin level less than 130 g/L in the first 24 hours of life indicates severe anemia, for which an RBC transfusion is generally recommended. It is also current practice to maintain the hemoglobin level greater than 130 g/L in neonates with severe respiratory or cardiac disease. While these practices seem logical, their efficacy remains to be established.⁹

Most RBC transfusions are given to replace phlebotomy losses for laboratory monitoring of ill premature infants or to treat clinically important problems attributed to the

physiologic decline in hemoglobin level that occurs after birth (anemia of prematurity). Precise indications for the use of RBCs in these two clinical settings have not been determined; however, the issues involved have been extensively reviewed.⁹⁻¹⁴

Phlebotomy losses are generally replaced after 5% to 10% of the infant's total blood volume has been removed. Although extensive blood loss in a sick infant may justify an RBC transfusion, the decision to transfuse should not be based exclusively on the quantity of blood removed. Other considerations include the age and clinical status of the neonate, the hemoglobin level at birth, and the length of time over which the losses have occurred.

Healthy preterm infants with a physiologic decline of hemoglobin level to 70 to 80 g/L do not require RBC transfusion in the absence of signs of anemia.^{13,14} However, it is difficult to define "signs of anemia" in the premature infant. Although most would include tachycardia, tachypnea, recurrent apnea, decreased vigor, and poor weight gain unexplained by other causes, controversy remains over the correlation of these signs and the response to RBC transfusions.⁹⁻¹⁹

Infants and Children 4 Months and Older

Guidelines for RBC transfusions in older infants and children are similar to those for adults (Table 2). In general, RBCs are indicated to (1) prevent or reverse tissue hypoxia due to a diminished RBC mass and/or (2) decrease endogenous (abnormal) hemoglobin production. In the assessment of the importance of any hemoglobin level in a child, it is important to remember that normal hemoglobin and hematocrit levels are lower in children than in adults.⁸ Indications for perioperative RBC transfusions are currently being reevaluated. The National Institutes of Health Consensus Development Conference convened to address this issue advocated an individualized approach.²⁰ Selected adult patients can be safely managed with an intraoperative hemoglobin level of 80 g/L.²¹ An individualized approach is especially important in pediatric practice, where most patients do not have associated cardiorespiratory diseases and likely do not require hemoglobin levels of greater than 100 g/L before, during, or after surgery. In particular, there should be a compelling reason to administer a postoperative RBC transfusion to a pediatric patient, as most children (without bleeding) can quickly restore their hemoglobin mass if given appropriate oral iron therapy.⁸

The development of guidelines for the replacement of acute blood loss due to nonsurgical bleeding is more difficult, because estimates of losses are frequently unreliable, and the diagnosis of impending shock in a child may be easily overlooked. The situation is further complicated by the wide range of values for heart rate and blood pressure in normal children. With adults, the most important measures in the treatment of acute hemorrhage are to control the hemorrhage and then to restore perfusion, usually with crystalloid and/or colloid. If the patient's condition remains unstable, then RBC transfusions are indicated.

In acutely ill patients with severe pulmonary disease requiring assisted ventilation, it is recommended that the hemoglobin level be maintained in the normal range.^{22,23} Although this recommendation may be valid, it has not been documented by scientific studies.

With anemias that develop slowly, the decision to administer RBCs to increase tissue oxygen delivery should

not be based solely on the hemoglobin concentration. Children with anemias that develop slowly may be asymptomatic despite hemoglobin levels well below 80 g/L. Patients with iron deficiency anemia, for example, often are treated with oral iron alone, even at hemoglobin levels below 50 g/L. Factors other than hemoglobin concentration to be considered in the decision to transfuse RBCs include (1) the patient's symptoms, signs, and functional capacities; (2) the presence or absence of cardiovascular, respiratory, or central nervous system disease; (3) the causes and anticipated evolution of the anemia; and (4) alternate therapies (and the ability to comply with them). In anemias that are likely to be permanent, one must also consider the effect of the anemia on growth and development as well as the effects of repeated transfusions.

Patients with sickle-cell diseases (SS, SC, or S β -thalassemia) without complications do not require RBC transfusions. However, there are several clinical settings in which these patients may require simple or partial exchange RBC transfusions to prevent tissue hypoxia and/or to suppress endogenous hemoglobin production.²⁴ A chronic RBC transfusion program is appropriate for patients with sickle-cell disease following a splenic sequestration crisis until splenectomy is performed (usually after 2 years of age)²⁵⁻²⁷ or following a cerebrovascular accident.²⁷⁻³³ There are no clear criteria to determine when it is safe to discontinue RBC transfusion following a cerebrovascular accident. Red blood cell transfusions may also be beneficial in the management of the following complications in patients with sickle cell diseases: acute chest syndrome, acute aplasia, priapism, and chronic leg ulcers.^{27,33,34-37} Although prophylactic RBC transfusions have frequently been used during pregnancy, a recent study has demonstrated that omitting them is not harmful to pregnant patients with sickle-cell disease or their offspring.³⁸ The optimal preoperative use of RBC transfusions has been extensively discussed in the literature.^{24,33,39-43} While most authors agree that the preoperative hemoglobin level should be 100 g/L, the issue of whether the hemoglobin S concentration should be lower than a predetermined level, eg, 30%, remains unresolved. Finally, RBCs are not indicated for patients with sickle-cell disease with uncomplicated episodes of pain.^{27,33}

Patients with severe thalassemia syndromes are placed on long-term RBC transfusion programs to prevent the consequences of severe anemia and ineffective erythropoiesis.⁸ The extent to which endogenous (ineffective) erythropoiesis is suppressed varies inversely with the minimum hemoglobin level achieved with the RBC transfusion program.⁴⁴ While most experts agree that the minimum pretransfusion hemoglobin level should be at least 90 g/L, there is controversy about the value of maintaining a higher minimum hemoglobin level.⁸

Red blood cell transfusions may also be given before renal transplantation to induce immune tolerance in patients with chronic renal failure.⁴⁵ However, in light of cyclosporine therapy, this indication for transfusion both in cadaveric and living related donor transplants is being reexamined.^{46,47}

TRANSFUSION OF PLATELET CONCENTRATES

Platelet transfusions are indicated for support of children with clinically important quantitative and/or qualitative platelet disorders (Table 3). Guidelines for children

Table 3.—Criteria for Transfusion of Platelet Concentrates*

Premature infants (gestational age <37 weeks)
1. Blood platelets <50 $\times 10^9$ /L in a stable infant
2. Blood platelets <100 $\times 10^9$ /L in a <u>sick</u> infant
All other infants and children
1. Blood platelet count <20 $\times 10^9$ /L and marrow failure
2. Blood platelet count <50 $\times 10^9$ /L with active bleeding or the need for an invasive procedure in a child with bone marrow failure
3. Blood platelet count <100 $\times 10^9$ /L with active bleeding plus disseminated intravascular coagulation or <u>other coagulation abnormalities</u>
4. Bleeding with <u>qualitative platelet defect</u> and <u>marked prolongation</u> of the bleeding time regardless of the platelet count
5. Cardiovascular bypass surgery with <u>unexplained excessive bleeding</u> , regardless of the platelet count

*Statements that are underlined require additional definition by each local transfusion committee.

are similar to those published for adults by a recent National Institutes of Health Consensus Conference on platelet transfusion therapy.⁴⁸

The risk of life-threatening hemorrhage, particularly intracranial hemorrhage, relates to the severity of thrombocytopenia. Studies in thrombocytopenic leukemic patients,⁴⁹ and in a thrombocytopenic dog model,⁵⁰ indicate that mucosal bleeding increases markedly when platelet levels fall below 20 $\times 10^9$ /L. For this reason, many physicians recommend prophylactic platelet transfusions to maintain a platelet count greater than 20 $\times 10^9$ /L in children with thrombocytopenia due to bone marrow failure. This recommendation is supported by the findings of at least one randomized study.⁵¹ When thrombocytopenia occurs in association with fever, active bleeding, the need for an invasive procedure, disseminated intravascular coagulation, or other severe clotting abnormalities, the "threshold" for platelet transfusions needs to be raised. Platelet transfusions should be used with caution and are generally contraindicated in the hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura, disorders caused by the formation of platelet thrombi in small vessels.

Platelet transfusions for the newborn infant merit separate consideration. Premature infants, particularly those who are ill, are at risk for intracranial hemorrhage. The incidence of this complication is higher in thrombocytopenic than in nonthrombocytopenic infants.⁵² Moreover, multiple abnormalities of hemostasis may be present in such infants. Thus, it is reasonable clinical practice to maintain a minimum platelet count of 50 $\times 10^9$ /L in premature infants, although this recommendation has not been proved scientifically. Until more data are available, the report from Andrew and colleagues⁵² suggests that the threshold for platelet transfusions in sick premature infants should be even higher, of the order of 100 $\times 10^9$ /L.

Neonatal alloimmune thrombocytopenia, a condition that reflects fetomaternal incompatibility for a platelet antigen, also deserves special consideration.⁵³ In more than 75% of cases, the pathologic platelet antibody demonstrates specificity for the platelet-specific antigen, Pl^{A1}.⁵⁴ The therapy of choice for affected infants with severe thrombocytopenia is the infusion of compatible platelets, obtained from the mother or a known antigen-negative

Table 4.—Criteria for Transfusion of Granulocyte Concentrates*

1. Bacterial sepsis in neonates <2 weeks of age with neutrophil plus band cell counts $<3 \times 10^9/L$
2. Bacterial sepsis unresponsive to antibiotics in patients >2 weeks of age with neutrophil plus band cell counts $<0.5 \times 10^9/L$
3. Documented infection(s) unresponsive to antibiotics plus a qualitative neutrophil defect, regardless of the neutrophil plus band cell count

*Statements that are underlined require additional definition by each local transfusion committee.

blood donor. If maternal platelets are used, it is important that they be irradiated and that maternal plasma containing pathologic platelet alloantibodies be removed from the platelet concentrate before transfusion.⁵⁵

Of the immune thrombocytopenic disorders encountered in pediatric practice, autoimmune thrombocytopenic purpura is the most common. In this disorder, platelets are rapidly destroyed by broadly reacting circulating platelet autoantibodies or immune complexes. The survival of donor platelets is markedly reduced, and there is general agreement that, except in the circumstance of life-threatening bleeding, platelet transfusions are not indicated. Alternate therapies (eg, steroids and high-dose intravenous IgG) are preferred.^{56,57} An analogous condition, neonatal autoimmune thrombocytopenia, occurs in infants delivered to affected mothers.⁵⁸ Thrombocytopenia in this disorder is self-limiting, and therapy is administered to minimize the risk of intracranial hemorrhage in severely thrombocytopenic infants. Similar to older children with autoimmune thrombocytopenic purpura, there is little rationale for use of platelet transfusions, and infants with severe autoimmune thrombocytopenia should receive intravenous IgG and/or steroid therapy.^{54,59}

Qualitative platelet disorders may be inherited or acquired, for example, in children with advanced hepatic or renal insufficiency or following cardiopulmonary bypass. In such patients, platelet transfusion therapy is justified if severe bleeding occurs. Prophylactic administration of platelets is not justified unless there are other conditions that interfere with hemostasis or if an invasive procedure is planned. In these cases, a bleeding time of greater than twice the upper limit of laboratory normal may be taken as justification for therapy,⁴⁸ and alternatives to platelet transfusions, particularly desmopressin acetate, should be considered.^{60,61}

It is easier to prevent than to stop bleeding in the thrombocytopenic patient. In children with uncomplicated thrombocytopenia due to bone marrow failure, 1 U per 10 to 15 kg is sufficient to prevent bleeding.⁶² Larger doses (1 U per 5 kg) may be required to achieve hemostasis in bleeding patients. It is common practice to limit the dose to 6 to 8 U of random donor platelets or one platelet pheresis concentrate (platelets obtained by apheresis of a single donor). The dose of platelets required to increase the platelet count to greater than $100 \times 10^9/L$ in newborn infants is 10 mL/kg of standard platelet concentrates prepared from single units of whole blood or by automated platelet pheresis (R. G. Strauss, MD, oral communication, 1990).

TRANSFUSION OF GRANULOCYTES

Granulocyte transfusions should be considered for infected pediatric patients in three clinical settings (Table 4).

Because some patients recover with antibiotics alone, institutions should survey the outcome of infections in neonates and neutropenic children treated locally. If the response to antimicrobial drugs alone is prompt and survival approaches 100%, granulocyte transfusions are unnecessary. However, if large numbers of patients fail to respond to antibiotic therapy, the addition of granulocyte transfusions should be considered.

During the first week of life, healthy neonates exhibit both neutrophilia and neutrophil functional abnormalities.⁶³ In infected neonates, neutrophil counts may fall to relatively "neutropenic" values of less than $3 \times 10^9/L$, with function thus deteriorating further.⁶⁴ At least 11 reports of granulocyte transfusions in neonates exist,⁶⁵ of which six are controlled studies.⁶⁶⁻⁷¹ Four of the six reported a markedly better outcome for neonates receiving antibiotics plus granulocyte transfusions prepared by automated leukapheresis than for neonates receiving antibiotics alone.⁶⁶⁻⁶⁹ In the two negative studies,^{70,71} low doses of neutrophils were transfused because they were isolated from buffy coats of whole blood, rather than by apheresis. Although data are inconclusive, sepsis is likely to be fatal in neonates with a fulminant clinical picture, blood neutrophil counts of less than $3 \times 10^9/L$, and evidence of a depleted bone marrow neutrophil storage pool.⁶⁴⁻⁶⁶ Granulocyte transfusions should be considered for these infants.

The role of granulocyte transfusions added to antibiotics for patients with severe neutropenia due to bone marrow failure is similar for both adults and children.⁷² Patients in most reports have been adults with leukemia or aplastic anemia, but five studies relate exclusively to children.⁷³⁻⁷⁷ Infected neutropenic patients usually respond to antibiotics alone, provided that bone marrow function recovers early in infection. Because children with newly diagnosed leukemia respond rapidly to induction chemotherapy, only rarely are they candidates for granulocyte transfusions. In contrast, infected children with sustained bone marrow failure (ie, malignant neoplasms resistant to treatment, aplastic anemia, and bone marrow transplant recipients) may benefit when granulocyte transfusions are added to antibiotics. The use of granulocyte transfusions for bacterial sepsis that is unresponsive to antibiotics in patients with severe neutropenia ($<0.5 \times 10^9/L$) is supported by most of the seven controlled studies reported to date.⁷⁸⁻⁸⁴

Patients with qualitative neutrophil defects (neutrophil dysfunction) usually have adequate numbers of blood neutrophils but are susceptible to serious infections because their cells kill pathogenic microorganisms inefficiently. Neutrophil dysfunction syndromes are rare, and no definitive studies have been reported to establish the efficacy of granulocyte transfusions. However, a few patients with progressive, life-threatening infections have improved strikingly with the addition of granulocyte transfusions.⁶⁵ These disorders are chronic, and granulocyte transfusions are recommended only when infections are clearly unresponsive to antimicrobial drugs.

Once the decision to provide granulocyte transfusions has been made, an adequate dose must be transfused. Neonates and infants weighing less than 10 kg should receive 1 to 2×10^9 neutrophils per kilogram per infusion. Larger infants and children should receive at least 1×10^{10} neutrophils per infusion; the preferred dose for adolescents is 2 to 3×10^{10} . Granulocyte transfusions should be con-

tinued daily until either the infection resolves or the blood neutrophil count rises to greater than $0.5 \times 10^9/L$.

TRANSFUSION OF FFP

The indications for FFP transfusion in children (Table 5) are similar to those reported for adults by the National Institutes of Health Consensus Development Conference addressing FFP transfusions.⁴ Transfusion of FFP is efficacious for the treatment of deficiencies of factors II, V, VII, X, XI, and XIII.

Requirements for FFP vary with the specific factor being replaced.⁸⁵ Transfusion of FFP is no longer recommended for the treatment of patients with hemophilia A or B, because safer factor VIII and IX concentrates are available for the treatment of these disorders. An important, albeit rare, use of FFP is for the rapid reversal of anticoagulant effect of warfarin sodium in patients who are actively bleeding or who require emergency surgery and in whom functional deficiencies of factors II, VII, IX, and X cannot be rapidly reversed by the administration of vitamin K.

In clinical practice, results of screening coagulation tests (prothrombin, activated partial thromboplastin, and thrombin times) are assumed to reflect the integrity of the coagulation system, and abnormalities are often used to justify FFP transfusion. However, test results must be related to the clinical condition of the patient. Transfusion of FFP in patients with chronic liver disease and prolonged screening coagulation test times are generally not recommended unless severe bleeding is present or an invasive procedure is planned. Fresh-frozen plasma transfusions in newborn infants merit special consideration; coagulation test times are prolonged in these infants,^{6,7} and FFP should only be transfused after reference to values expected for the particular patient. The indications for FFP in neonates have been reviewed⁸⁶ and include (1) reconstitution of RBC concentrates to whole blood in the setting of massive transfusions (for example, exchange transfusion or cardiovascular surgery), (2) hemorrhage secondary to vitamin K deficiency, (3) disseminated intravascular coagulation (although exchange transfusion is more often used than simple transfusion), and (4) bleeding in a patient with a congenital coagulation factor deficiency when more specific treatment is either unavailable or inappropriate. The use of prophylactic FFP transfusions to prevent intraventricular hemorrhage in premature infants is controversial,⁸⁷⁻⁸⁹ so a firm recommendation about this practice cannot be made. Although still being used to adjust the hematocrit values for small-volume RBC transfusions to neonates, FFP offers no apparent medical benefit⁹⁰ and exposes the infant to an additional donor. This practice should be discouraged. In addition, its use in partial exchange transfusion for the treatment of neonatal hyperviscosity syndrome is unnecessary, as safer colloid solutions are available.⁹¹

While its major benefit has been in the treatment of bleeding associated with coagulation factor deficiencies, FFP also contains several anticoagulant proteins (antithrombin III, protein C, and protein S) whose deficiencies have been associated with thrombosis.⁹² In selected situations, FFP may be appropriate as replacement therapy in patients with these disorders.⁹³ An alternative is a commercially produced concentrate.^{94,95}

Other indications for FFP include replacement fluid during plasma exchange in patients with thrombotic thrombocytopenic purpura or other disorders in which FFP is

Table 5.—Criteria for Transfusion of Plasma Products*

Fresh-frozen plasma

1. Bleeding, or an invasive procedure, in a patient with a coagulation factor deficiency or a markedly prolonged prothrombin, and/or partial thromboplastin times
2. Replacement therapy in antithrombin III or protein C or S deficiencies
3. Replacement therapy during therapeutic plasma exchange for disorders in which fresh-frozen plasma is beneficial

Cryoprecipitate

1. Bleeding, or an invasive procedure, in hemophilia A or von Willebrand's disease
2. Bleeding, or an invasive procedure, in hypofibrinogenemia or dysfibrinogenemia
3. Replacement therapy in factor XIII deficiency

Clotting factor concentrates

1. Bleeding, active or anticipated, in patients with documented coagulation factor deficiencies, such as hemophilia A or B
2. Severe or variant forms of von Willebrand's disease

Albumin

1. Acute correction of hypoalbuminemia when clinically indicated
2. Correction of hypovolemia when colloid infusion is indicated
3. Replacement therapy in therapeutic plasma exchange procedures

*Statements that are underlined require additional definition by each local transfusion committee.

beneficial.^{96,97} Fresh-frozen plasma transfusions are not indicated for correction of hypovolemia or as immunoglobulin replacement therapy, because safer alternatives exist.⁹⁸

TRANSFUSION OF CRYOPRECIPITATE

Cryoprecipitate, prepared by thawing FFP at 4°C, is still used by some hemophilia programs for factor replacement of patients with hemophilia A or von Willebrand's disease. A refinement that is sometimes used is the preparation of cryoprecipitate following repetitive plasmapheresis of selected donors.⁹⁹ Alternatives to cryoprecipitate include desmopressin acetate (for patients with mild to moderate hemophilia A or von Willebrand's disease) or specific clotting factor concentrates.¹⁰⁰⁻¹⁰²

Other uses for cryoprecipitate include correction of hypofibrinogenemia or dysfibrinogenemia and replacement therapy in patients with factor XIII deficiency.¹⁰³ Its use to provide fibronectin, a substance with opsonic activity, in patients with, or at risk for, bacterial sepsis (eg, premature infants) remains uncertain.¹⁰⁴

TRANSFUSION OF CLOTTING FACTOR CONCENTRATES

Factor VIII and IX concentrates are used as replacement therapy in patients with hemophilia A and B. The introduction of commercial concentrates into North America in the late 1960s markedly improved the treatment of patients with these inherited coagulation disorders. They made possible the development of cost-effective home therapy programs¹⁰⁵ and allowed severe hemophiliacs a degree of freedom previously not possible. For this advance, hemophiliacs have paid a high price. The majority who received repeated infusions of factor VIII or IX concentrates of

Table 6.—Criteria for Transfusion of Cytomegalovirus Low-Risk Blood Products in Seronegative Patients

1. Recipients of seronegative kidney, heart, heart-lung, or liver organ grafts
2. Recipients of seronegative bone marrow
3. Patients who are likely candidates for bone marrow transplantation
4. Pregnant women and their fetuses, if intrauterine transfusions are required
5. Neonates weighing ≤ 1250 g at birth
6. Patients infected with the human immunodeficiency virus

North American origin now manifest clinical and/or serologic evidence of infection with the hepatitis and acquired immunodeficiency syndrome viruses, reflecting the fact that these concentrates are prepared from pools of thousands of plasma units. Fortunately, a number of effective virus inactivation processes (super dry heat, vapor heat, pasteurization, and solvent-detergent treatment) can now be applied to factor concentrates during the manufacturing process, and the newer concentrates carry an extremely low risk of transmitting known infections, such as acquired immunodeficiency syndrome or hepatitis.¹⁰⁶⁻¹⁰⁹ Until factors VIII and IX produced by recombinant DNA technology become available, these new plasma-derived factor concentrates are the treatment of choice for patients with severe hemophilia A or B (Table 5).

Other clotting-factor concentrates in current use include both activated and nonactivated prothrombin complex concentrates for the management of bleeding in patients with hemophilia A and a circulating inhibitor^{110,111} and concentrates that are known to contain the multimeric forms of von Willebrand factor in patients with von Willebrand's disease.^{112,113}

TRANSFUSION OF ALBUMIN

The major uses of albumin are listed in Table 5.¹¹⁴ The most common is for the correction of hypovolemia when colloid infusion is indicated.¹¹⁵ Administered with a diuretic, albumin is also used for the acute correction of hypoalbuminemia in the treatment of fluid overload¹¹⁵ and in postburn fluid resuscitation.¹¹⁶ It is routinely used as replacement fluid with normal saline for most therapeutic plasma exchange procedures.⁹⁶

Albumin is available as both a 5% and 25% solution. Plasma protein fraction is equivalent to 5% albumin but is subject to fewer purification steps and in the past has been associated with more adverse reactions.¹¹⁷

TRANSFUSION OF CYTOMEGALOVIRUS (CMV) LOW-RISK BLOOD PRODUCTS

Cytomegalovirus is an ubiquitous herpes virus harbored in the white blood cells of donor blood. In the immunocompromised host, posttransfusion CMV may cause further immunosuppression, placing the patient at substantial risk for morbidity or mortality. Immunocompromised groups of patients at risk for posttransfusion CMV¹¹⁸⁻¹²² are listed in Table 6. These groups are candidates for CMV low-risk (eg, seronegative) blood products. In addition, it may be prudent to transfuse CMV low-risk products until the serologic status of the following patients is known: (1) premature infants weighing less than 1250 grams at birth,

Table 7.—Criteria for Transfusion of Irradiated Blood Products*

1. Bone marrow transplant recipients
2. Neonates and children with severe known or suspected congenital or acquired immunodeficiency states
3. Fetuses who require intrauterine transfusions
4. Neonates who received intrauterine transfusions and who require transfusions postnatally
5. Recipients of cellular blood products from first-degree relatives

*Statements that are underlined require additional definition by each local transfusion committee.

(2) patients with malignant neoplasms who are likely candidates for bone marrow transplantation, and (3) patients infected with the human immunodeficiency virus type 1.

There is no evidence to support the use of CMV low-risk blood products either in seropositive oncology or in solid organ transplant patients who are receiving immunosuppressive drug regimens or in other seropositive subjects.

Current practice is to utilize IgG CMV seronegative blood and blood products, with the knowledge that only a fraction of IgG seropositive units are infectious. Tests to detect IgM antibodies or CMV viral antigens are not yet sufficiently developed to replace IgG testing. Other methods to decrease CMV transmission include extreme leukodepletion of blood products by filtration or following freeze-thawing and washing.¹²³ Use of frozen deglycerolized washed RBCs, regardless of donor serology, has been demonstrated to reduce posttransfusion CMV in renal allograft recipients, post-cardiac surgery patients, and premature infants. Whether leukodepleted RBCs are a viable alternative to the use of CMV IgG-negative RBC merits further study.¹²⁴ Measures to reduce the risk of CMV transmission need only be applied to cellular blood products (RBCs, platelets, and granulocytes); FFP and cryoprecipitate are sufficiently acellular that CMV transmission does not present a substantial clinical problem.

TRANSFUSION OF IRRADIATED BLOOD PRODUCTS

Graft-vs-host disease occurs when donor-derived T cells engraft in an immunoincompetent recipient. Clinically important graft-vs-host disease is a rare complication^{125,126} that occurs from 3 to 30 days (median, 8 days) following transfusion. It has been observed following transfusion of whole blood, RBCs, buffy coats, fresh plasma, and granulocyte or platelet concentrates but not following transfusion of cryoprecipitate or frozen plasma, probably because component preparation reduces the concentration of functional lymphocytes to less than the number critical to induce graft-vs-host disease.¹²⁷

Posttransfusion graft-vs-host disease follows an acute course and is frequently fatal, especially in infants and children, in whom 80% to 90% mortality rates have been reported.¹²⁵ Because there is no effective treatment, the goal is to (1) recognize clinical conditions in which posttransfusion graft-vs-host disease is likely to occur, (2) employ techniques to eliminate its cause, and (3) ensure that the techniques used do not adversely affect the product to be transfused. Patients at risk should receive blood products processed to remove functional T cells or to render such cells ineffective. Filtration, sedimentation, freeze-thawing, or washing with current methods has the undesired potential to leave enough T cells to induce graft-vs-host disease or to render the product inadequate for

transfusion. Current practice utilizes ionizing radiation from a cesium, cobalt, or linear acceleration source at doses ranging from 1500 to 5000 cGy to protect against graft-vs-host disease. A dose of 1500 cGy is most frequently used.^{128,129} Patients at risk for graft-vs-host disease (Table 7) should receive irradiated blood products.

Premature infants are known to have immune dysfunction, but their risk of acquisition of posttransfusion graft-vs-host disease is not well established. The postnatal age of the infant, number of immunocompetent lymphocytes in the transfusion product, degree of HLA compatibility between donor and recipient, and other as yet poorly described phenomena may determine which infants should receive such products.¹³⁰ Directed donations with blood from first-degree relatives should be irradiated because of the risk of engraftment with HLA haploidentical lymphocytes in these products.^{131,132} Other groups potentially at risk, but for whom no data are available, are those receiving T-cell depletion therapy (antithymocyte globulin or OKT3) and recipients of organ transplantation who are receiving chronic T-cell suppressive drug regimens.

The following persons served on the Pediatric Hemotherapy Committee during conduct of this project: Asa Barnes, Jr, MD; Christine Barrasso, MT(ASCP) SBB; Janice F. Blazina, MD; Lynn Black, MS, MT(ASCP) SBB; Susanne Butch, MT(ASCP) SBB; Ann McMican, MT(ASCP) SBB; Cirilo Sotelo-Avila, MD; Kenneth Starling, MD; Alice Werner, MD; and Alvin M. Mauer, MD (liaison from the American Academy of Pediatrics).

We thank Maureen Andrew, MD, Nancy Olivieri, MD, and Jutta Preiksaitis, MD, for their helpful comments during preparation of the manuscript, and Nancy Fair for excellent secretarial assistance. The manuscript was prepared with the assistance of Medical Publications, The Hospital for Sick Children, Toronto, Ontario.

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PedvaxHIB®

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INDICATIONS AND USAGE: PedvaxHIB is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease, such as meningitis or sepsis.

Revaccination: Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use with Other Vaccines: Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) (using separate sites and syringes), or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine or the diluent.

WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: General: As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

Age (Months)	Reaction	Number of Subjects Evaluated	Dose 1			Number of Subjects Evaluated	Dose 2		
			6 hr.	24	48		6 hr.	24	48
2-14*	Fever >38.3°C (101°F)	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
	Rectal	149	4.0%	4.0%	6.7%				
15-71**	Fever >38.3°C (101°F)	572	0.0%	0.3%	0.2%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				
	Rectal								

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against Haemophilus b disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group (see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792—PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797—PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.

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JVOA08(802)

The Effect of Low-Dose Dopamine Infusion on Cardiopulmonary and Renal Status in Premature Newborns With Respiratory Distress Syndrome

Lily Cuevas, MD; Tsu F. Yeh, MD; Eunice G. John, MD; Danilo Cuevas, MD; Rosita S. Plides, MD

● To study the effects of infusion of low doses of dopamine hydrochloride on cardiopulmonary and renal status in premature newborns with respiratory distress syndrome, 49 newborns were randomly assigned to three groups: group 1 (18 patients) received no dopamine and was the control group; group 2 (16 patients) was infused with a dose of dopamine measuring 1.0 $\mu\text{g/kg}$ of body weight per minute for 72 hours; and group 3 (15 patients) was infused with a dose of dopamine measuring 2.5 $\mu\text{g/kg}$ of body weight per minute for 72 hours. Birth weights, gestational ages, post-natal ages, and cardiopulmonary status of all groups at the start of the study were comparable. Continuous infusion of these low doses of dopamine for 3 days after birth did not significantly improve levels of blood gases, acid-base balance, or clinical outcome. In newborns with systemic hypotension, dopamine improved cardiovascular status and caused early return of blood pressure to the normal range. Infusion of low doses of dopamine produced mild to moderate natriuresis and insignificant increases in glomerular filtration rate and urine volume.

(AJDC. 1991;145:799-803)

Pulmonary edema sometimes occurs in the early stages of respiratory distress syndrome (RDS) in premature newborns. Although the causes are many, vasoregulatory disturbances and poor renal function are important causes of the fluid accumulation associated with pulmonary edema.^{1,2} Dopamine hydrochloride, infused in low doses, has recently been shown effective in improving circulation and promoting diuresis in premature newborns.³⁻⁵ This prospective study investigates whether early and continuous infusion of low doses of dopamine during the first 3 days after birth improves outcome in premature newborns with RDS.

Accepted for publication August 20, 1990.

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Presented in part before the Society for Pediatric Research, Washington, DC, May 7, 1987.

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PATIENTS AND METHODS

This study was approved by the scientific and lay committees of the Cook County (Illinois) Hospital, Chicago, and informed consent was obtained from the parents of each participant.

Between October 1986 and September 1987, 60 newborns whose birth weights ranged from 700 to 2000 g were included in

Table 1.—Perinatal Characteristics and Biochemical Data of Patients*

	Group 1	Group 2	Group 3
Birth weight, g	1289 \pm 320	1178 \pm 187	1190 \pm 272
Gestational age, wk	31 \pm 2.0	30 \pm 1.9	31 \pm 1.4
Type of delivery			
Natural spontaneous vaginal delivery	12	12	10
Cesarean section	6	4	5
Apgar score, No. of patients			
≤ 3	3	4	4
4-6	12	11	10
> 6	3	1	1
Age at time of study, h	5.8 \pm 1.4	6.0 \pm 1.5	5.6 \pm 1.4
Biochemical level at time of study			
Mean airway pressure, cm H ₂ O	10.1 \pm 1.9	10.6 \pm 3.2	10.1 \pm 2.4
Fractional inspired oxygen	0.54 \pm .23	0.60 \pm .26	0.66 \pm .25
PO ₂ , mm Hg	74.0 \pm 48.8	99.4 \pm 87.3	110 \pm 77.7
PCO ₂ , mm Hg	36.5 \pm 7.4	33.7 \pm 8.3	32.0 \pm 8.5
pH	7.36 \pm 0.07	7.39 \pm 0.06	7.39 \pm 0.08
Blood pressure, mm Hg			
Systolic	46.9 \pm 10.5	42.3 \pm 6.9	43.4 \pm 7.0
Diastolic	30.0 \pm 10.4	30.4 \pm 7.3	24.7 \pm 8.4
Mean	37.0 \pm 8.2	36.0 \pm 7.0	33.0 \pm 6.4
Heart rate, beats/min	142.6 \pm 9.4	141.6 \pm 8.4	144.6 \pm 10.8

*Values are means \pm SDs.

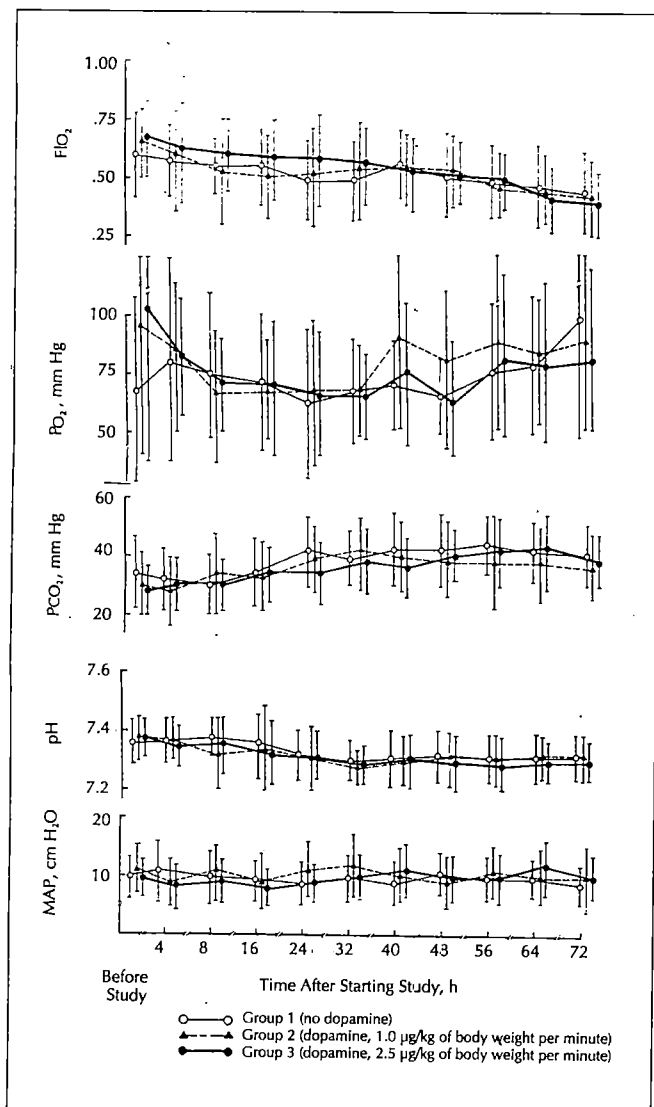


Fig 1.—Blood gases, pH, and mean airway pressure (MAP) of mechanical ventilation during the study.

the study. Inclusion required that newborns have clinical and radiologic evidence of RDS and that they received mechanical ventilation within 4 hours of birth. On inclusion, the newborn was randomly assigned to one of the following three groups: group 1, in which patients were not administered dopamine; group 2, in which patients were administered dopamine in doses of 1.0 µg/kg of body weight per minute for 72 hours; and group 3, in which patients were administered dopamine in doses of 2.5 µg/kg of body weight per minute for 72 hours. Each group comprised 20 newborns. During the study, dopamine was infused through a peripheral vein by an intravenous pump (Micro Flo-gard 8500, Travenol, Deerfield, Ill). Dopamine was administered through an umbilical arterial catheter when no peripheral vein was accessible.

All newborns were treated using a standard protocol previously reported from our nursery.⁶ The protocol emphasized the criteria for initiation of and weaning from mechanical ventilation and intake of fluids and electrolytes. Blood gas samples were obtained before the study began and every 4 hours after from an umbilical arterial catheter or a radial artery. Occasionally, blood gas samples were obtained by the arterialized capillary method; in these cases, only pH and PCO₂ levels were included for data analysis. The PO₂ values were then obtained by the transcutaneous method (TcPO₂) (Radiometer Copenhagen TCM2 Transcutaneous Monitor, Radiometer, Copenhagen, Denmark). Blood

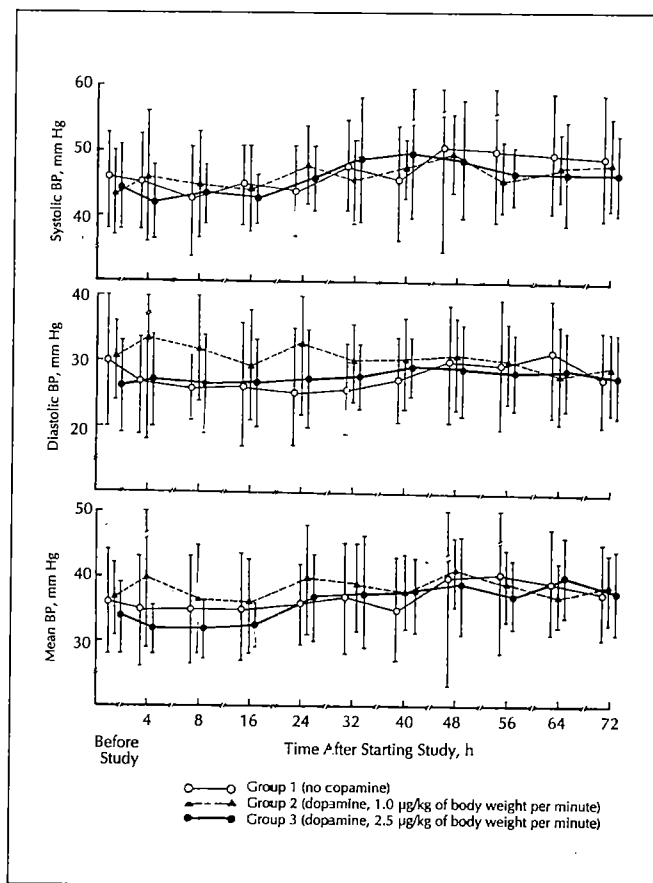


Fig 2.—Systolic, diastolic, and mean blood pressure (BP) during the study.

pressure was continuously monitored through an umbilical arterial catheter on a multiple-channel neonatal monitor (HP 78834 A; Hewlett Packard, Palo Alto, Calif). Arterial hypotension was diagnosed as systolic blood pressure at least 10 mm Hg below the predicted normal value for gestational and postnatal age.^{7,8}

During the study period, fluid intake was adjusted to 80, 95, and 110 mL/kg of body weight per day on days 1, 2, and 3, respectively. An additional 20 mL/kg of body weight per day was given if the infant was receiving phototherapy. The intravenous fluids consisted of 10% dextrose in water during the first day and 5% dextrose with electrolytes (25 mmol of sodium per liter of water and 20 mmol of potassium per liter of water) thereafter. No oral or nasogastric feeding was administered during the study period, and none of the newborns received diuretics or aminophylline.

All newborns were kept in incubators, and their skin temperatures were maintained by servocontrol at 36.5°C. Urine was collected in three aliquots 0 to 24, 24 to 48, and 48 to 72 hours after starting the study by attaching a U-bag (Hollister, Chicago, Ill) to the perineum. Suprapubic compression was performed at the beginning and end of each collection to ensure that the bladder was empty. The urine samples and the corresponding timed serum specimens were measured for electrolytes, creatinine, and osmolality. The glomerular filtration rate (GFR) or creatinine clearance; fractional excretion of sodium (FE_{Na}), chloride (FE_{Cl}), and potassium (FE_K); and osmolality (Cosm) and free water clearance (C_{H₂O}) were all calculated using the conventional formulas.⁶

After completion of the study, all newborns were treated using a standard protocol currently used in our neonatal intensive care unit. Presumptive diagnosis of chronic lung disease was made if the infant had respiratory distress that required oxygen therapy and had an abnormal chest roentgenogram by the criteria of Northway et al.⁹ Mortality rate and duration of oxygen therapy were also assessed.

Table 2.—Characteristics of Renal Function*

	Group No.	Time After Starting Study, h		
		0-24	24-48	48-72
Urine output, mL/kg of body weight per hour	1	2.9±1.9	4.8±2.4	4.2±2.4
	2	2.6±1.3	3.8±2.1	3.1±1.1
	3	2.3±1.2	3.2±1.6	2.9±1.5
Glomerular filtration rate, mL/min per 1.73 m ²	1	5.5±3.2	6.5±3.7	8.6±5.4
	2	5.1±1.9	8.4±5.2	7.6±3.2
	3	4.3±3.7	6.1±4.7	6.1±3.8
Fractional excretion of sodium, %	1	2.1±1.3	5.1±4.2	3.9±2.8
	2	6.6±4.4 †	6.7±4.1 ‡	6.7±5.0 ‡
	3	3.7±2.7	4.5±3.2	4.8±2.8
Fractional excretion of chloride, %	1	2.1±1.3	5.4±4.7	4.2±3.1
	2	5.0±3.2	6.0±4.7	6.5±4.8
	3	2.7±2.4	4.2±3.2	5.1±3.1
Fractional excretion of potassium, %	1	28.8±15.9	34.6±20.7	36.9±34.8
	2	39.6±19.4	45.3±35.2	36.4±22.9
	3	34.7±21.2	33.3±15.0	36.6±14.6
Osmolar clearance, mL/min per 1.73 m ²	1	.25±.13	.49±.23	.51±.30
	2	.60±.32†	.72±.34‡	.70±.26‡
	3	.24±.24	.33±.22	.39±.32
Free water clearance, mL/min per 1.73 m ²	1	.21±.13	.41±.22	.41±.35
	2	.56±.30‡	.66±.32	.64±.26
	3	.21±.24	.25±.25	.34±.31

*Values are means±SDs.

†*P*<.05, group 2 vs group 1.

‡*P*<.01, group 2 vs group 1.

The Student's *t* test was used to compare the continuous variable between the groups, and the χ^2 test to compare categorical variables between groups. The values were expressed as means±SDs. Except where otherwise indicated, the time discussed in the text was the time after entry into the study.

RESULTS

Sixty newborns were enrolled in the study, 20 in each group. Three newborns in group 2 and four newborns in group 3 were excluded from the study because of skin blanching around the infusion site. Two newborns in group 1 and one newborn each in group 2 and group 3 died of severe RDS shortly after the study began. The final numbers of newborns included for data analysis were 18 in group 1, 16 in group 2, and 15 in group 3. The perinatal characteristics and the biochemical data of all patients at entry into the study are shown in Table 1. No significant difference in any of these variables was shown.

Ventilator Set-up, Blood Gases, and Acid-Base Balance

While no significant difference was evident between the groups in mean airway pressure (Fig 1) and peak inspiratory pressure at any time during the study, newborns in group 2, compared with those in group 1, required significantly lower ventilatory rates 4 and 8 hours after entering into the study (36±12/breaths per minute vs 50±11/breaths per minute and 36±13/breaths per minute vs 49±14/breaths per minute, respectively). Ventilatory rates of groups 1 and 3 were comparable. No significant difference was evident between the groups in incidence of extubation after 72 hours (two in group 1, four in group 2, and three in group 3). Except for a temporary higher P_{O_2} in group 2 than

in group 1 after 40 hours, F_{IO_2} , P_{CO_2} , and pH did not significantly differ between the groups during the study.

Blood Pressure and Heart Rate

The systolic, diastolic, and mean blood pressure changes in the groups are shown in Fig 2. The groups did not significantly differ in any of these variables during the study.

Renal Function

Glomerular filtration rate (creatinine clearance) and levels of urine output, fractional excretion of electrolytes, and C_{H_2O} and C_{Cosm} clearance are shown in Table 2. Urine volume increased as a function of age in all three groups. The increase in urine volume was onefold to twofold higher in groups 2 (120%) and 3 (90%) than in group 1 (65%) after 24 to 48 hours. The same trend, but of a lesser magnitude, was noted in groups 2 (50%) and 3 (60%) compared with group 1 (44%) after 48 to 72 hours. None of these changes were significant owing to a wide variation in individual values.

Glomerular filtration rates also increased in all three groups of newborns as a function of age. After 24 to 48 hours, the incremental change in GFR from baseline values after 0 to 24 hours was 3.6 and 2.3 times greater in groups 2 (65%) and 3 (42%), respectively, than in group 1 (18%). A similar trend of increased GFR, but to a lesser extent, was noted in groups 2 and 3 after 48 to 72 hours. However, these changes were not statistically significant.

In groups 1 and 3, increases in levels of FE_{Na} were noted after 24 to 48 and 48 to 72 hours compared with baseline values after 0 to 24 hours. These changes were not significant, but consistent. Group 2 newborns had significantly higher levels of FE_{Na} after 0 to 24, 24 to 48, and 48

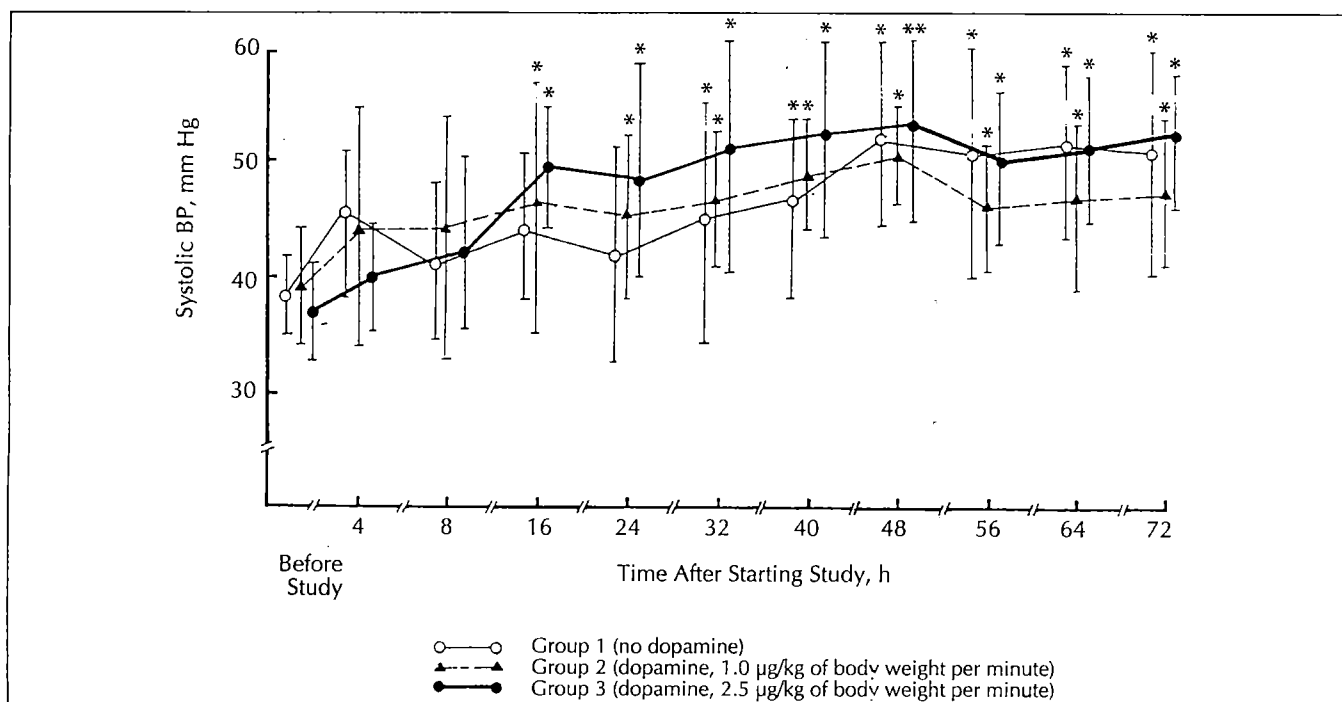


Fig 3.—Changes in systolic blood pressure (BP) after starting the study in infants who showed initial systemic hypotension. Asterisk indicates $P < .05$, compared with baseline. Double asterisks indicate $P < .01$, compared with baseline.

to 72 hours compared with group 1 newborns. Similar changes were noted in levels of FE_{Cl} and $Cosm$ in group 2 newborns (Table 2).

Free water clearance also increased as a function of age, but these changes were less obvious in group 3 than in groups 1 and 2. Because these newborns were not loaded with water, interpretation of C_{H_2O} values should be made with caution. Significantly higher levels of C_{H_2O} were noted in group 2 than in group 1 throughout the study.

Levels of FE_K were not significantly different among groups or in each group compared with baseline values.

Newborns With Systemic Hypotension

Seven newborns in group 1, eight in group 2, and six in group 3 had systemic hypotension when the study began. A significant rise in systolic BP from baseline values to predicted normal values was seen after about 16 hours in groups 2 and 3 and after 32 hours in group 1 (Fig 3). However, no significant difference was evident between the groups during the study in FIO_2 , Pco_2 , pH, and in all parameters of ventilator set-up. Except for transient higher levels of $Cosm$ and C_{H_2O} after 4 hours in group 2 than in groups 1 and 3, GFR and levels of urine output and fractional excretion of electrolytes did not significantly differ among groups.

Clinical Outcome

No significant difference was evident between groups 1, 2, and 3 in mortality (five of 18, four of 16, and four of 15, respectively), chronic lung disease among surviving newborns (five of 13, four of 12, and five of 11, respectively), and duration of oxygen therapy (30 ± 18 , 26 ± 25 , and 32 ± 29 days, respectively).

COMMENT

This study demonstrates that continuous infusion of low doses of dopamine ($1 \mu\text{g/kg}$ of body weight per minute

and $2.5 \mu\text{g/kg}$ of body weight per minute) during the first 3 days after birth in premature newborns with RDS did not significantly improve levels of blood gases, acid-base balance, or clinical outcome. In newborns with RDS and systemic hypotension, administration of dopamine improved cardiovascular status by producing early return of blood pressure to the normal range. Infusion of low doses of dopamine produced mild to moderate natriuresis and subtle but nonsignificant increases in levels of GFR and urine volume. Considering these findings, we do not recommend general use of dopamine in newborns with RDS.

The systemic and renal effects of dopamine are complex and related to dose and age. Because sympathetic innervation may be incomplete in developing animals and newborn humans,¹⁰ responses to dopamine may be different from those in adults. In preterm neonates, low doses of dopamine have pronounced effects on α and dopamine receptors, while it only minimally stimulates β receptors.¹¹ In addition to the difference in vascular receptor maturation, decreased metabolic clearance of dopamine⁵ also should be considered when explaining cardiovascular and renal effects of the drug. Dopamine has been found useful in improving impaired peripheral circulation and producing diuresis in hypotensive preterm newborns with severe hyaline membrane disease and oliguria.^{3,4} In these newborns, the effects of low doses of dopamine ($2 \mu\text{g/kg}$ of body weight per minute) were assessed after the intravenous infusion of plasma protein (1 g/kg of body weight to 2 g/kg of body weight). Dopamine produced only transient increases in systolic BP.^{3,4} In our study, administration of dopamine in doses of $1 \mu\text{g/kg}$ of body weight per minute and $2.5 \mu\text{g/kg}$ of body weight per minute did not significantly increase BP when data for all patients in each group were considered. However, the return of blood pressure to normal range in hypotensive newborns was

similar to that noted by Seri et al.³ They noted sustained and significant increases in blood pressure only after increasing the dopamine dosage to 2 µg/kg of body weight per minute. Because most of our patients were normotensive, had only mild to moderate RDS, and received only maintenance fluid, low doses of dopamine did not have an obvious effect on their blood pressures. Thus, low doses of dopamine may play a modulating role depending on the basal condition in a given newborn and may be most effective only in hypotensive patients. Seri et al also noted tachycardia during dopamine infusion only with doses of 8 µg/kg of body weight per minute.³ In our patients, administration of low doses of dopamine (1 µg/kg of body weight per minute and 2.5 µg/kg of body weight per minute) had no effect on heart rate, a result that was also noted by Seri et al.³

The natriuretic effect of dopamine depends on its direct enhancement of renal blood flow and GFR, and inhibition of sodium absorption by the tubules and on its indirect inhibition of salt-retaining hormones such as aldosterone¹² and prolactin.¹³ Studies by Jose et al¹⁴ on the effects of catecholamines, including dopamine, on renal function during neonatal development indicate that the low renal blood flow of newborns is due to increased effects of α-adrenergics and decreased effects of dopaminergics.^{14,15} Similar observations were made by Buckley et al¹⁶ in newborn pigs. Felder et al¹⁷ observed that the natriuretic and renal vasodilatory effects of dopamine also increase with age.

Alpha-adrenergic blockade increased sodium excretion in puppies and adult dogs. A greater effect was observed in older puppies. The addition of β-adrenergic blockade did not change levels of sodium excretion in younger puppies. These physiologic properties were related to low densities of β-adrenoreceptors and high densities of α-adrenoreceptor in renal tubular membranes.¹⁷ In adults, low doses of dopamine (1 to 8 µg/kg of body weight per minute) may increase renal blood flow. In puppies, dopamine administered in doses of 5 to 10 µg/kg of body weight per minute decreased the rate of renal blood flow and GFR and increased levels of FE_{Na} .

In our studies, GFR and urine volume increased as a function of age in all three groups. However, increases in GFR were of greater magnitude in newborns who received dopamine. The nonsignificant increase in GFR and urine volume shown in this study compared with other studies^{4,14} that have shown significant increases in GFR and natriuresis was most probably due to variation in values caused by age-related changes and differences in basal conditions. It is also possible that low doses of dopamine exert beneficial effects on GFR and urine volume only in patients with oliguria and impending renal failure and/or hypotension. Our patients had no evidence of impending renal failure or oliguria, and only a few patients had hypotension without administration of intravenous fluid boluses. Our studies were conducted for 72 hours, while other studies were conducted for only a few hours.⁴

In group 2 newborns, levels of FE_{Na} , FE_{Cl} , and $Cosm$ increased significantly compared with levels in group 1 newborns despite nonsignificant increases in GFR and urine volume. This increase in sodium excretion could have been due mainly to dopamine's direct and indirect effects on tubules and partly to minor increases in GFR. In our patients, the natriuretic effect of higher doses of dopamine (2.5 µg/kg of body weight per minute) was less

prominent than that of lower doses (1 µg/kg of body weight per minute). These results are different from other studies in which diuresis and natriuresis were noted with administration of both high and low doses.^{3,4} It is possible that group 3 newborns were volume-depleted compared with newborns in groups 1 and 2, as proved by low levels of C_{H_2O} in group 3 newborns after 24, 48, and 72 hours. On the other hand, delayed clearance of dopamine and high plasma concentration may have decreased the effects of renal dopaminergics and increased the effects of α-adrenergics. The blunted natriuretic effect of dopamine in group 3 newborns also could have been due to different basal conditions such as intravascular volume¹⁸, levels of plasma aldosterone,¹² prolactin,^{13,18} and vasopressin¹⁹; and sensitivity of renal α receptors vs dopaminergic receptors. Because we did not measure levels of plasma aldosterone, prolactin, or vasopressin, these possibilities remain speculations.

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Effect of Necrotizing Enterocolitis on Urinary Epidermal Growth Factor Levels

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• The pattern of urinary epidermal growth factor/creatinine levels in necrotizing enterocolitis was examined in 75 infants (in 28 infants the diagnosis of necrotizing enterocolitis was considered; 47 infants were studied for effect of surgery or nutrition on epidermal growth factor levels). There was a consistent and significant increase in epidermal growth factor/creatinine values at the time of diagnosis of necrotizing enterocolitis compared with baseline values. Epidermal growth factor levels in infants without necrotizing enterocolitis and in early nutrition remained unchanged. These results suggested that urinary epidermal growth factor/creatinine levels may differentiate stage II and III necrotizing enterocolitis from stage I disease. The increased epidermal growth factor/creatinine levels may be related to the absorption into the circulation of preexisting gastrointestinal tract epidermal growth factor through damaged tissue or to increased synthesis by the gastrointestinal tract in response to the injury caused by necrotizing enterocolitis.

(AJDC. 1991;145:804-807)

Epidermal growth factor (EGF) is a polypeptide that may be involved in the growth and differentiation of the gastrointestinal tract.¹ Exogenous EGF enhances gut enzyme activity² while maintaining proliferation of the intestinal mucosa during total parenteral nutrition.³ Epidermal growth factor may be available to the gut via the saliva,⁴ breast milk,⁵ and probable endogenous gastrointestinal tract synthesis.⁶ In the mature animal, EGF appears to function primarily during periods of injury,⁷ while the intact gastrointestinal tract has been inconsistently demonstrated to be responsive to the oral administration of EGF.^{8,9}

Although the role of EGF in healing has been studied primarily using skin¹⁰ and cornea,¹¹ recently Wright et al¹² described new EGF synthesis sites near ulcer formations in patients with Crohn's disease, and Grotendorst et al¹³

demonstrated EGF-like activity in wound fluid. In the neonatal period, the most prevalent gut injury is related necrotizing enterocolitis (NEC).¹⁴ Necrotizing enterocolitis is distinguished from immature gut motility and absorption abnormalities by its association with the loss of mucosal integrity and tissue destruction.^{15,16} As such, NEC serves as a human model of gastrointestinal injury in which early healing is needed for recovery.¹⁷

Because of EGF's role in healing and the evidence of early healing in the process of NEC, we hypothesized that at the time of diagnosis, EGF levels would be elevated in infants with NEC in contrast to levels in infants with abnormalities of gut motility.

SUBJECTS AND METHODS

Subjects and Samples

All infants admitted to the Newborn Intensive Care Unit at the Children's Hospital of New Mexico, Albuquerque, were eligible for the study. The research protocol was approved by the Human Research Review Committee of the University of New Mexico School of Medicine and parental informed consent was obtained prior to the collection of urine samples. As part of a developmental urinary EGF study, a urine sample was collected within 24 hours of birth and then at least weekly unless the diagnosis of NEC was considered by the attending neonatologist. Daily urine samples were then collected until the diagnosis was ruled out or the therapy for NEC was completed. Some of the infants who required surgical therapy had urine samples collected until closure of their enterostomy.

Infants with NEC were staged according to the criteria of Bell et al.¹⁸ Criteria for a diagnosis of stage I (suspect) disease included mild ileus on roentgenography with clinical evidence of feeding intolerance, temperature instability, lethargy, apnea, and/or bradycardia. Criteria for stage II (definite) disease also included gastrointestinal bleeding and abdominal roentgenograms that show bowel wall separation suggesting edema, pneumatosis intestinalis, or portal vein gas. A diagnosis of stage III (advanced) disease included the above criteria as well as deterioration of vital signs and/or evidence of septic shock. Abdominal roentgenograms may demonstrate pneumoperitoneum.

A separate group of infants had urine samples collected daily for 14 days to explore the acute effect of initiation of nutrition on EGF excretion. Day-1 EGF values were compared 2 days after initiation of oral alimentation and at age 10 days, correlating to the period during which NEC was noted in the study group. The effect of surgery was also explored in infants who had a surgical ligation of a patent ductus arteriosus. All samples were separated into two aliquots and frozen at -20°C for measurement of human EGF and creatinine.

Accepted for publication January 28, 1991.

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Presented in part at the Western Society of Pediatric Research meeting, Carmel, Calif, February 9, 1989, and the Society for Pediatric Research meeting, Washington, DC, May 2, 1989.

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Table 1.—Patient Clinical Description*

	Stage of NEC		
	I	II	III
Sample size	15	5	8
No. F/M	6/9	2/3	4/4
Gestational age, wk	24-42	28-32	24-40
No. SGA/AGA	1/8	0/5	4/4

*NEC indicates necrotizing enterocolitis; SGA, small for gestational age; and AGA, appropriate for gestational age.

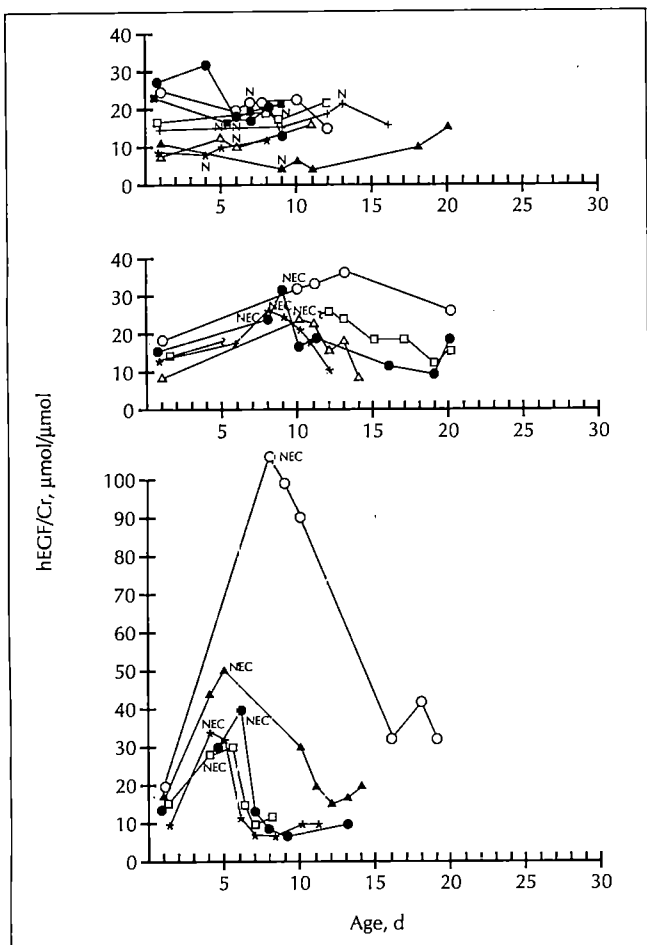


Fig 1.—Top, Human epidermal growth factor/creatinine (hEGF/Cr) values in eight of 15 infants with stage I necrotizing enterocolitis (NEC) (from Table 2). N indicates days feedings were withheld. The last sample was collected on the day that feedings were reinitiated. Middle, EGF values in the five infants with stage II NEC (from Table 2). NEC indicates day that the diagnosis was made. Bottom, EGF values in the five infants with stage III NEC (from Table 2). NEC indicates day that the diagnosis was made.

EGF Assay and Creatinine Measurements

Antibodies to human EGF were raised in white New Zealand rabbits using recombinant human EGF. The recombinant form of human EGF had biological activity similar to that of the native hormone.¹⁹ Our radioimmunoassay, as previously reported,²⁰ used human recombinant EGF for antigen and for use in antibody production. Human EGF was stored at -20°C for use in a standard curve ranging from 10 ng through 0.01 ng. Urine control samples were added to every 50th tube. Human EGF was iodinated with fresh iodine 125 (ICN Biomedical, Inc, Irvine, Calif) using chloramine-T.²¹ Repurification was done on a size separation column (Sephadex G = 25, Sigma Chemical Co, St Louis,

MO) before use in each assay. The homologous EGF radioimmunoassay was run as a discontinuous assay beginning on day 1 with first antibody, normal rabbit serum, bovine serum albumin, and phosphate-buffered saline added to the tubes for the standard curve and the samples to be tested. On day 3, EGF with iodine 125 was added to each tube at 10 000 counts per minute. On day 4, a second antibody (goat, antirabbit immunoglobulin antibody) was added, followed by polyethylene glycol. The samples were centrifuged (TJ-6, Beckman Centrifuge, Palo Alto, Calif) at 1500g for 30 minutes, and the supernatant was decanted. The pellet was counted (Searle gamma counter, Des Plaines, Ill) for 1 minute. Nerve growth factor (Sigma Chemical Co), insulin (Sigma) and transforming growth factor α (Calbiochem, La Jolla, Calif) did not cross-react in the assay at a hundredfold molar excess. Human EGF values were expressed in micrograms per liter. Creatinine levels were measured using the picric acid method.²² Creatinine values were expressed in millimoles per liter and EGF/creatinine (EGF/Cr) values in micrograms per millimole.

Statistical Analysis

Epidermal growth factor/creatinine values in individual patients were examined with paired *t* tests for values before and after an episode of NEC and compared with the values at the time of diagnosis of NEC. One-way analysis of variance and paired *t* tests were used to examine the effect of nutrition and the effect of patent ductus arteriosus ligation surgery on EGF excretion, respectively. Comparisons between groups in which the diagnosis of NEC was considered were performed using the two-way analysis of variance followed by the Neuman-Kuel test, which demonstrates significance for unpaired results. The values at diagnosis were also compared with baseline values by percent of change from baseline, and groups were compared using unpaired *t* tests.

RESULTS

Patients

During the period from January 1986 to December 1988, the diagnosis of NEC was considered in 53 infants. We have chosen to discuss in depth only those 28 infants who presented at less than 2 weeks of age. This decision was made because of the postnatal developmental urinary EGF/Cr pattern. Epidermal growth factor/creatinine levels are relatively stable prior to age 2 weeks²³; there is a dramatic change beginning at age 4 weeks. The absolute EGF/Cr values of the infants with NEC who were older than 2 weeks were thus different from the EGF/Cr values of the younger infants, but the change from baseline remained comparable. The values in the older infants are not included in the results.

Clinical information on the 28 infants is presented in Table 1. All of the 15 infants with stage I disease survived and were refeed 1 to 5 days after the diagnosis of NEC was entertained. None progressed to stage II or III disease. All of the five infants with stage II disease continued receiving total parenteral nutrition for 7 to 10 days and were treated with intravenous antibiotics and gastric suctioning. Each of the eight infants with stage III disease manifested clinical deterioration and required operation for damaged gut. All eight infants survived.

In the older group not described in detail, three infants with stage III disease died. The changes in EGF/Cr values from baseline in those three infants were the lowest of all 13 infants with stage III disease, although they were not significantly different (eight at less than 2 weeks and five at more than 2 weeks).

EGF Values

The first three rows of Table 2 display the mean (\pm SEM) EGF/Cr values for the stages of NEC. Epidermal growth

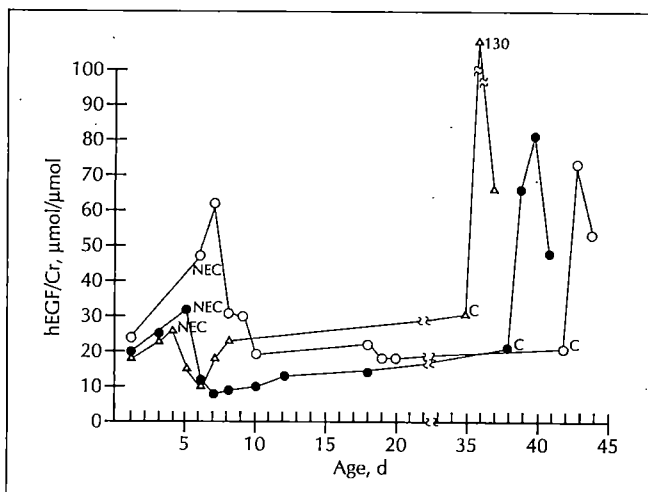


Fig 2.—Human epidermal growth factor (hEGF) levels in three infants followed up from birth until closure of an enterostomy. NEC indicates day that the necrotizing enterocolitis was diagnosed, and C, the day that the enterostomy was closed.

factor/creatinine values for infants with stage I disease did not demonstrate a significant change from baseline. There was a significant increase in EGF/Cr values for each patient with stage II ($P < .01$) or stage III ($P < .005$) NEC compared with values before and after the course of NEC, with an increase in EGF/Cr values for each infant ranging from 1.1 to 1.5 and 1.5 to 5.0 times above baseline values for stage II and stage III disease, respectively. There were no significant differences in the EGF/Cr values at diagnosis between patients with stages II and III NEC. The data were converted to percent change from baseline to remove the effect of the wide range of baseline values on statistical evaluation. The groups were still not statistically different ($P = .06$).

Figure 1 displays the EGF/Cr patterns for each stage of NEC. Baseline EGF values were related to gestational age and gender. Our studies have demonstrated higher EGF/Cr levels in female infants and increasing cross-sectional levels with advancing gestation.²³ There was no consistent change in EGF/Cr values in the group with stage I NEC related to the withdrawal of oral nutrition, which is the time of initiation of daily sampling and/or reinitiation of enteral feeding (upper panel). Epidermal growth factor/creatinine values for only eight of 15 infants are displayed for visual clarity. The EGF/Cr values for the other seven were not different from those displayed. For infants with stage II and stage III NEC, increased EGF/Cr values were noted on two sequential days. There was a consistent increase in EGF/Cr values in infants with stage II (middle panel) disease at diagnosis, and levels appeared to stay elevated longer than in patients with stage III disease. For stage III disease, data on all infants who did not require an enterostomy are displayed (lower panel). The increase in EGF/Cr levels usually occurred on the same day as surgery. Values dropped consistently after resection of damaged bowel.

Thirteen infants had urine samples collected for EGF/Cr levels concomitant with a surgical procedure. Values did not significantly change for the 10 infants who underwent a surgical ligation of a patent ductus arteriosus (18.4 ± 9.1 $\mu\text{mol}/\text{mmol}$ before surgery and 17.3 ± 7.4 $\mu\text{mol}/\text{mmol}$ 1 day after ligation). Figure 2 shows the EGF/Cr values in the three infants with NEC for whom samples were available when their enterostomy was closed. Epidermal

Table 2.—Urinary Epidermal Growth Factor Values During Necrotizing Enterocolitis*

	Epidermal Growth Factor Values, $\mu\text{mol}/\mu\text{mol}$		
	Before	During	After
Stage I (n = 15)	17.5 ± 4.0	20.3 ± 2.8	21.0 ± 2.4
Stage II (n = 5)	15.0 ± 1.6	$33.1 \pm 5.2^\dagger$	18.0 ± 4.1
Stage III (n = 5)	13.9 ± 7.8	$45.8 \pm 25.4^\ddagger$	16.3 ± 5.8
Oral (n = 27)	14.9 ± 8.9	15.9 ± 10.3	13.5 ± 12.3
Parenteral (n = 10)	16.4 ± 9.3	12.3 ± 5.5	8.9 ± 3.2

*Before represents sample taken at birth; during, sample taken on the day of diagnosis; and after, sample taken on the day nutrition was reinitiated for stages of necrotizing enterocolitis. For oral and parenteral values, before, at birth, and during represent day 6 and after day 10. Values are means \pm SEMs.

$^\dagger P < .01$ for values during necrotizing enterocolitis vs those before and after.

$^\ddagger P < .005$ vs values before and after necrotizing enterocolitis.

growth factor/creatinine levels increased in each infant at the time NEC was diagnosed and decreased after surgical resection. At the time of enterostomy closure, urinary EGF/Cr concentrations had been stable for several days. Within a few days of closure of the enterostomy, the urinary EGF/Cr levels dramatically increased, and then with further sampling, EGF/Cr levels began to decrease again.

Epidermal growth factor samples were collected from 37 infants to examine the effect of nutrition on EGF/Cr levels. Feedings were initiated by 1 week (Table 2) in 27 infants and no significant changes were noted in EGF/Cr levels during this period. Ten infants received no oral nutrition for longer than 1 week of life with sepsis as their primary diagnosis. Their EGF/Cr values at 1 week were significantly decreased from day 1 ($P < .05$).

COMMENT

Our results suggested that infants who present with stage II and III NEC during the first 2 postnatal weeks have elevated urinary EGF/Cr levels at the time of diagnosis compared with infants without bowel injury. The causes of this increase are unknown. There were no discernible acute effects of surgery on urinary EGF levels, which is consistent with the findings of Abe et al²⁴ in adult patients. Some renal dysfunction may have occurred in this group of ill infants. We have previously demonstrated²⁰ that congenital renal disease significantly decreased urinary EGF/Cr levels, and others have also described decreased EGF excretion in acquired renal disease,²⁵ suggesting that our results are not related to renal dysfunction.

A consistent change in EGF/Cr levels could be related to a change in nutrition. Gale et al²⁶ demonstrated increased urinary EGF/Cr levels in preterm infants receiving oral nutrition compared with those receiving total parenteral nutrition. Our results demonstrated that there was a significant decrease in EGF/Cr values when oral nutrition was not initiated by 1 week. Thus, the initial acute increase in EGF/Cr levels with stages II and III NEC was not consistent with interruption of oral alimentation.

The urinary EGF/Cr pattern in stage II disease may be related to the greater production of factors involved in healing. These infants may have less severely damaged tissue that has not been removed but would then require or stimulate a constant release of factors for healing. The study of Crohn's disease demonstrated the development of a novel cell lineage that secreted EGF in response to

chronic ulcer formation.¹¹

The urinary EGF pattern in infants with stage III disease may initially reflect the absorption of EGF through a damaged bowel into the circulation, reflecting the loss of gastrointestinal barrier to absorption of proteins.²⁷ With removal of the bulk of diseased tissue followed by a prolonged cessation of oral nutrition, EGF values would drop quickly. The prolonged increase in EGF excretion from baseline in infants with stage II disease would then suggest continued absorption through the diseased bowel.

The acute increase in EGF levels after closure of the enterostomies was unanticipated. If EGF is lost through an enterostomy and is also needed for healing, gastrointestinal tract EGF production may be enhanced. With closure of the enterostomy, an increased load of EGF may be present and may lead to an acute, short-term absorption through newly anastomosed tissue.

Finally, evidence of absorption of EGF through an intact bowel into the blood stream was demonstrated by Thornburg et al.²⁸ and urinary excretion of blood-borne EGF was described by Jorgensen et al.²⁹ These results, combined with the loss of the gastrointestinal barrier to absorption of proteins and the demonstration of EGF production both in wound fluid and specifically in the ulcerated gut, suggest that the changes in EGF levels we describe with definite NEC are not unexpected.

Extremely low-birth-weight infants are at high risk of feeding intolerance and comprise the group in whom the most consistent nutrition is desirable. Also, concerns for NEC are greatest in this group. A marker that could distinguish definite NEC from bowel dysfunction may result in fewer significant interruptions in oral alimentation. Further studies are needed to define the role of EGF in the process of NEC and to clarify the usefulness of EGF as a biochemical marker of true bowel disease. Thus, although measurement of EGF remains a research tool, it may become clinically important in the treatment of the extremely low-birth-weight infant.

This work was funded in part by Basic Science grant 1-1034 from the March of Dimes, chronic disease grant 042-022-87 from the Flinn Foundation, and grant NIH 5 MOIRR00997-13 from the General Clinical Research Program, DDR, National Institutes of Health, Bethesda, Md. Dr Scott is a recipient of a Clinical Investigator Award from the National Institutes of Health.

Recombinant human EGF was donated by Carlos George-Nascimento, PhD, and Pablo Valenzuela, PhD, at the Chiron Corporation, Emeryville, Calif.

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Neutropenia in an Extremely Premature Infant Treated With Recombinant Human Granulocyte Colony-Stimulating Factor

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● Neutropenia in the newborn is often associated with sepsis, maternal hypertension, or prematurity. We describe a 654-g infant born at 30 weeks' gestation by cesarean section due to severe maternal hypertension. His course was complicated by five episodes of sepsis, including three with group B streptococcus. The results of hematologic and immunologic studies were normal except that absolute neutrophil counts were low ($<1 \times 10^9/L$) with intermittent increases during sepsis. Human recombinant granulocyte colony-stimulating factor administered subcutaneously (10 $\mu g/kg$ per day initially) resulted in an absolute neutrophil count of greater than $30 \times 10^9/L$ within 2 weeks. The dosage was lowered and the absolute neutrophil counts were maintained at 8 to $12 \times 10^9/L$ with no further septic episodes. The human recombinant granulocyte colony-stimulating factor therapy was discontinued after 7 months, and the patient remained healthy with an absolute neutrophil count of greater than $2 \times 10^9/L$. Thus, treatment with human recombinant granulocyte colony-stimulating factor may be useful as a temporary measure for neonatal neutropenia associated with sepsis. A controlled, clinical trial is warranted.

(AJDC. 1991;145:808-812)

Neutropenia in the newborn may be associated with bacterial sepsis, transplacental transfer of maternal antineutrophil antibodies, toxemia of pregnancy, and rare congenital defects in myelopoiesis.¹⁻⁷ In many cases, there is no clear cause of the neutropenia, although the decreased number of myeloid precursor cells in the normal newborn's marrow compared with adults puts the infant at much greater jeopardy of becoming neutropenic. The most common organism associated with overwhelming sepsis in the newborn is group B streptococcus (GBS),

which continues to produce significant mortality despite modern antibiotic therapies.

Thus, the decrease in circulating neutrophils, the diminished myeloid reserve in the marrow, and the immaturity of the immune system of the newborn make these infants susceptible to life-threatening bacterial infections when neutropenic. These problems are accentuated by prematurity, although the neutropenia will usually resolve in both term and premature infants if they survive the early complications.

Treatment has been limited in most cases to supportive therapy with antibiotics to treat the infection when the infant is septic. Granulocyte transfusions have been used with some success, but frequent infusions are required due to the short half-life of neutrophils, and the patient is exposed to blood products from several donors with the associated risks.^{8,9} Intravenous γ -globulin may be beneficial for immune-mediated neutropenia but it is ineffective for other forms.^{10,11} Bone marrow transplantation has been used to treat specific forms of congenital neutropenia, such as Kostmann's syndrome, but it requires the identification of a suitable donor and further immunosuppression in an already immunocompromised infant.¹²

Several human hematopoietic growth factors that mediate proliferation and maturation of myeloid cells have been cloned with recombinant DNA technology and are now used in clinical trials.^{13,14} One of these cytokines, recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF), specifically stimulates the maturation of myeloid bone marrow cells into neutrophils.¹⁵ This cytokine has been used in patients with Kostmann's syndrome and idiopathic and cyclic neutropenia.¹⁶⁻¹⁸ Patients with these forms of neutropenia have responded to r-metHuG-CSF with increased neutrophil counts and decreased infections. However, daily injections are required indefinitely to maintain the neutrophil count, and the neutropenia recurs when drug therapy is discontinued. To our knowledge, r-metHuG-CSF has not been used to treat transient neutropenia in neonates.

We describe the use of r-metHuG-CSF in an extremely premature, neutropenic infant who had experienced multiple episodes of bacterial sepsis, including three episodes

Accepted for publication January 28, 1991.

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Presented in part at the annual Society of Pediatric Research meeting, Anaheim, Calif, May 10, 1990.

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Infectious Episodes Before r-metHuG-CSF Therapy*

Date	Source	Organism	Absolute Neutrophil Count (No. $\times 10^9/L$)	
			Before Therapy†	After Therapy‡
6/03/89	Blood, cerebrospinal fluid, urine, tracheal aspirate	<i>Staphylococcus aureus</i>	0.72	3.588
6/12/89	Blood	Coagulase-negative staphylococcus	2.835	7.938
7/01/89	Tracheal aspirate	Group B streptococcus	0.752	1.581
7/24/89	Blood	Group B streptococcus	1.484	4.554
8/12/89	Nasal swab	Group B streptococcus	0.555	6.278
8/23/89	Blood	Group B streptococcus	1.504	7.150

*r-metHuG-CSF indicates recombinant human granulocyte colony-stimulating factor.

†Twenty-four to 48 h before antibiotic therapy started.

‡Twenty-four to 72 h after antibiotic therapy started.

of GBS. This patient's neutropenia was not characteristic of Kostmann's syndrome or immune-mediated forms, but the pregnancy was complicated by severe maternal hypertension. The patient's neutrophil count rose dramatically and he experienced no further septicemia after the initiation of r-metHuG-CSF therapy. This patient, in addition to being the youngest patient, to our knowledge, to be treated with this cytokine, also differed from previously reported cases of congenitally neutropenic patients in that his neutrophil count was maintained when the r-metHuG-CSF was discontinued.

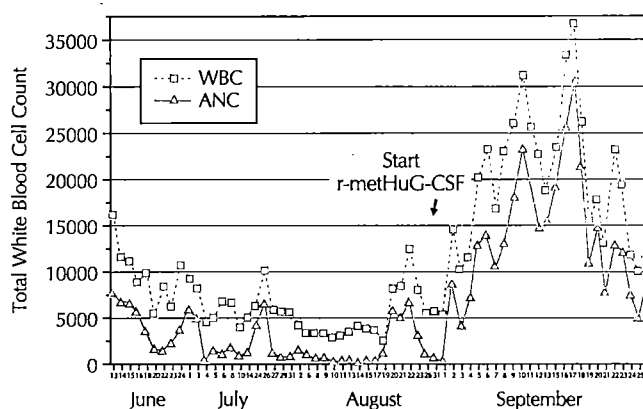
MATERIALS AND METHODS

The r-metHuG-CSF (Amgen, Thousand Oaks, Calif) used had been molecularly cloned from human cells and successfully expressed in *Escherichia coli* by Souza et al.¹⁵ Highly purified HuG-CSF and the recombinant product have been shown to have identical in vitro biological activity.¹⁹

The nitroblue tetrazolium test to assess oxidative potential of neutrophils was performed on neutrophils separated from blood on gradients (Percoll, Pharmacia Fine Chemicals, Uppsala, Sweden). The cells were activated in suspension with phorbol myristate acetate (20 mg/L) and adhered to a glass slide by centrifugation. The slides were counterstained with safarine dye and the percentage of nitroblue tetrazolium-positive cells (those staining blue due to dye reduction) was determined with light microscopy.

Immunofluorescence and flow cytometry were used to detect the presence of antineutrophil antibodies in the patient's serum (Specialty Labs, Santa Monica, Calif). Neutrophils from a normal donor were incubated in a patient's serum, and fluorescently tagged rabbit antihuman IgG antisera was then employed to detect IgG on the neutrophil surface.

Flow cytometry performed by the Clinical Immunology Research Laboratory at UCLA was used to determine lymphocyte subsets (based on surface antigens CD3, CD4, CD8, and CD19). Flow cytometry using a flow cytometer (FACScan, Becton-



Total white blood cell (WBC) count and absolute neutrophil count (ANC) before and after recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF) therapy. The increases in WBC count and ANC on June 24, July 24, and August 21 before r-metHuG-CSF therapy were associated with septic episodes. The initial dose of 10 $\mu g/kg$ per day was gradually decreased; by day 20 the dose was 1 $\mu g/kg$ per day due to the high ANC.

Dickinson, Mountain View, Calif) determined the presence and density of the CD11b (C3bi receptor) antigen on the surface of the neutrophils. The patient's neutrophils were assessed for the presence of the CD11b antigen both at a baseline state (blood kept at 4°C) and following stimulation with the peptide formyl-methionyl-leucyl-phenylalanine at 37°C.

REPORT OF A CASE

A 654-g boy was born at 30 weeks' gestation by cesarean section to a 38-year-old primigravida white woman. The pregnancy had been induced by in vitro fertilization, and the mother had suffered severe pregnancy-induced hypertension. The patient had an Apgar score of 8/9 at 1 and 5 minutes. He required intubation for apnea on the first day of life, and routine supportive care was initiated. Blood, cerebrospinal fluid, and urine cultures taken 3 days later were positive for *Staphylococcus aureus*. During the next 3 months, the patient suffered four additional episodes of sepsis despite treatment with appropriate courses of antibiotics and multiple infusions of intravenous γ -globulin. The causal agents included *Staphylococcus epidermidis* and three episodes of GBS sepsis, all of the same phage type.

The patient was noted to be neutropenic, with an absolute neutrophil count (ANC) of less than $1 \times 10^9/L$ at age 3 days. The ANC rose to between 7 and $8 \times 10^9/L$ by age 2 weeks, but then dropped to less than $1 \times 10^9/L$ by age 4 weeks. The patient continued to have periods of neutropenia, with intermittent increases in his ANC to 3 to $8 \times 10^9/L$ when septic (Figure).

These recurrent septic episodes and neutropenia prompted an immunologic evaluation. The patient's neutrophil oxidative respiratory burst activity was evaluated with the nitroblue tetrazolium test and the results were normal, with greater than 95% of cells staining blue, indicating dye reduction. Complement activity, as assessed with erythrocyte hemolysis (CH100), was within normal limits, as were quantitative levels of the complement components C3 and C4 (0.74 g/L and 0.24 g/L, respectively). Analysis of lymphocyte subsets showed them to be normal for gestational age, with 61% total T cells (CD3), 39% T helper cells (CD4), 11% T suppressor cells (CD8), and 24% B cells (CD20). Antineutrophil antibodies were not detected in the patient's serum by immunofluorescence assays performed using flow cytometry.

In flow cytometric assays, the baseline CD11b expression of the patient's neutrophils were within the range obtained using normal adult donors. Following stimulation with formyl-methionyl-leucyl-phenylalanine, neutrophils from both patients and controls showed an approximately 20-fold increase in antigen density of CD11b.

Intravenous γ -globulin had been initiated as a prophylactic measure to prevent sepsis (500 mg/kg per day for 5 days and 500 mg/kg weekly thereafter). The intravenous γ -globulin did not increase the patient's ANC or prevent new septic episodes. The intravenous γ -globulin and maternally transferred immunoglobulin hampered assessment of the patient's own ability to make IgG antibody, although his IgM level was 0.22 g/L at 3 months, which is normal for gestational age.

Bone marrow biopsy of the right iliac crest under general anesthesia revealed a few myeloid cells in various stages of maturation. Although the specimen was not optimal because of the technical difficulty involved in obtaining marrow from a premature infant, there was no evidence of a myeloproliferative disorder. Amniocentesis performed during the pregnancy had shown the normal male chromosome number (46,XY) and morphologic structure, but the bone marrow specimen was not adequate for chromosomal analysis.

Repeated cranial ultrasonography showed no evidence of periventricular or intraventricular hemorrhage. The patient appeared neurologically intact and in clinically stable condition between his septic episodes.

Because the patient's neutropenia appeared to precede his septicemia (Table), we believed that he might benefit from treatment with r-metHuG-CSF. His parents concurred with this therapeutic plan, and informed consent was obtained under a protocol approved by the UCLA Human Subjects' Protection Committee.

RESULTS

Within 24 hours of receiving an initial subcutaneous injection of 10 μ g/kg of r-metHuG-CSF at age 3 months, the patient's white blood cell count rose dramatically from $5.8 \times 10^9/L$, with a differential cell count of 0.12 segmented neutrophils, no bands, and an ANC of $0.70 \times 10^9/L$, to a white blood cell count of $14.9 \times 10^9/L$ with 0.32 segmented neutrophils, 0.29 band cells, and an ANC of $9.09 \times 10^9/L$ (Figure). As the white blood cell count climbed to a peak of $37 \times 10^9/L$, with a corresponding ANC of $26 \times 10^9/L$, the daily dose of r-metHuG-CSF was gradually decreased. A maintenance dose of 1 μ g/kg per day was reached on day 20 of therapy, and the white blood cell count was stabilized at between 10 and $20 \times 10^9/L$, with an ANC of 8 to $15 \times 10^9/L$.

A slight increase in irritability that was noted at the highest dose of r-metHuG-CSF (10 μ g/kg) resolved at the lower dose. This irritability may have been due to bone pain reported by older patients in clinical trials of r-metHuG-CSF.^{16,18} The patient had no evidence of infection for the remainder of his hospitalization. He was discharged 24 days after starting r-metHuG-CSF therapy of diuretics, theophylline, and oxygen by nasal cannula for his bronchopulmonary dysplasia.

Approximately 1 week after discharge, the patient was readmitted to UCLA for respiratory distress secondary to fluid overload. He remained afebrile; cultures of blood, cerebrospinal fluid, and urine were negative and a chest roentgenogram was consistent with chronic bronchopulmonary dysplasia. The patient was discharged after 5 days when his pulmonary status had improved.

The remainder of the patient's course was unremarkable except for three episodes of otitis media that were treated with oral antibiotics. He did not show any evidence of allergic or other adverse reactions to the r-metHuG-CSF. His quantitative immunoglobulin levels were normal for a person aged 10 months, and the functional status of his B cells was verified by a protective antitetanus toxoid titer following immunization. Abdominal ultrasonography did not show any abnormal enlargement of the spleen.

Six months after starting treatment, the patient continued to maintain an ANC of between 8 and $12 \times 10^9/L$ while receiving 1 μ g/kg per day of r-metHuG-CSF. The dosage was reduced to 0.5 μ g/kg per day for 2 weeks, and the patient remained in clinically stable condition, with no significant drop in ANC. The r-metHuG-CSF was completely discontinued after 7 months of treatment, and the patient remained in clinically stable condition, with an ANC of greater than $2 \times 10^9/L$ and with no infections 6 months after the drug therapy was discontinued.

COMMENT

Neonatal sepsis is thought to be a major cause of neonatal neutropenia, as determined by the absolute number of circulating neutrophils and their bone marrow precursors in the newborn. However, in a review by Baley et al,¹ fewer than half of 119 prospectively identified episodes of neutropenia in 37 infants could be attributed to sepsis. Other forms of neutropenia seen in the newborn include autoimmune and isoimmune neutropenia (analogous to Rh isoimmunization), congenital neutropenia (autosomal recessive or dominant), and neutropenia secondary to exchange transfusion or drug ingestion. Maternal hypertension,³ prematurity,² periventricular hemorrhage,²⁰ severe asphyxia,⁴ and extracorporeal membrane oxygenation²¹ have also been associated with neonatal neutropenia. In one third of the cases of neonatal neutropenia, no cause of the neutropenia was identified.¹ Thus, the clinical cause of a low neutrophil count in the neonatal period is not clear in many cases.

Newborns have a much greater tendency to develop neutropenia when septic owing to their low bone marrow reserve of myeloid cells.^{5,22} Christensen et al²³ examined the marrow of a series of neutropenic neonates and reported that only one of nine survived when the marrow was depleted of mature neutrophils. Neutropenia associated with recurrent episodes of sepsis that persists despite antibiotic therapy merits further investigative studies.

Kostmann's syndrome, or severe congenital neutropenia, is an autosomal recessive disorder in which the ANC is chronically less than $0.2 \times 10^9/L$, and bone marrow examination reveals arrested development at the promyelocyte or myelocyte stage. Most patients develop fatal infections in childhood, although a few have been treated with bone marrow transplantation.¹²

Maternal hypertension is often associated with newborn neutropenia, particularly in premature infants. In a recent study of 72 infants whose mothers experienced hypertension during pregnancy, 35 (49%) had neutropenia, which was more profound in those born prematurely or growth retarded in utero. Kinetic evaluation of neutrophil storage, margination, and proliferation suggests that diminished production is responsible for neutropenia in these newborns,⁷ and evidence exists of an inhibitory factor produced by the placenta.²⁴ The neutropenia resolved in 83% of these infants within 60 hours after birth, and no infant was neutropenic for more than 30 days.

Two recombinant hematopoietic growth factors, r-metHuG-CSF and granulocyte macrophage (GM) CSF, have been used in clinical trials for the treatment of primary neutropenia. Although both of these cytokines stimulate neutrophils, GM-CSF also enhances proliferation of monocytes and eosinophils.²⁵ Granulocyte macrophage

colony-stimulating factor has been used effectively in patients with aplastic anemia, chemotherapy-induced myelosuppression, autologous bone marrow transplants, and myelodysplastic syndrome.²⁶⁻²⁹ When GM-CSF was used to treat one patient with congenital neutropenia associated with a myeloid maturation defect, the result was a profound increase in circulating eosinophils and monocytes but little change in neutrophils.³⁰ Other investigators^{31,32} have also found that in patients with congenital neutropenia, GM-CSF has a much more pronounced effect on eosinophils than neutrophils.

Prior investigations using r-metHuG-CSF in the pediatric population have focused on treatment of severe congenital and cyclic neutropenia. In a study by Bonilla et al,¹⁶ patients with congenital agranulocytosis (Kostmann's syndrome) responded to r-metHuG-CSF by an increase in their ANC from less than $0.1 \times 10^9/L$ to between 1.3 and $9.5 \times 10^9/L$ 8 to 9 days after the appropriate dose was administered. Marrow aspirates from treated patients showed maturation to the mature neutrophil stage. Side effects of treatment included medullary pain, splenomegaly, and elevated levels of leukocyte alkaline phosphatase. Clinically, chronic infections resolved and the number of new infectious episodes as well as the requirement for intravenous antibiotics decreased.

Hammond et al¹⁷ and others³³ found that mean neutrophil counts in patients with cyclic neutropenia increased following r-metHuG-CSF therapy. Although cycling of blood cell counts continued, the length of the cycling period decreased from 21 to 14 days and the frequencies of fever, infection, and mouth ulcers were also reduced. This cytokine has also been used successfully to treat idiopathic neutropenia¹⁸ and myelodysplastic syndromes.^{34,35} Treatment of these forms of neutropenia as well as Kostmann's syndrome and cyclic neutropenia may require indefinite administration of r-metHuG-CSF since the ANC decreases abruptly when the drug therapy is discontinued.

The cause of the neutropenia in the infant described herein is unclear, although this case demonstrated multiple factors that could be implicated, such as bacterial sepsis, maternal hypertension, and prematurity. The absence of antineutrophil antibodies and the lack of response to intravenous immunoglobulin make it unlikely that there was an immune-mediated destruction of his neutrophils. Maternal hypertension is often associated with neonatal neutropenia, but in a recent report by Koenig and Christensen,⁷ the neutropenia resolved by age 30 days. Our patient continued to be neutropenic 3 months after birth.

Our patient also experienced multiple episodes of bacterial sepsis, the most commonly reported association with neutropenia. However, his neutropenia often preceded the sepsis, and the ANC actually rose during the septic episode, although not to markedly high levels. This infant's extreme prematurity (654 g at birth) also put him at greater risk of neutropenia. Although full-term infants have been reported to have high levels of G-CSF and GM-CSF at birth, the levels in premature infants are unknown.³⁶ It has been suggested that in some patients with congenital neutropenia the defect is in the G-CSF receptor on the myeloid cells rather than in decreased G-CSF production.^{16,37} However, our patient's very rapid and profound increase in ANC after receiving just one dose of r-metHuG-CSF suggests that his cells were responding ap-

propriately to the drug. Thus, there is no single factor to which we can attribute neutropenia in this patient.

The increased susceptibility of GBS sepsis in newborns is believed to be due to both a decreased neutrophil reserve as well as qualitative defects in the function of neonatal neutrophils.³⁸ Cairo et al³⁹ showed that simultaneous administration of r-metHuG-CSF and antibiotics to neonatal rats inoculated with GBS increased survival to 91%, compared with a 28% survival rate with antibiotics alone and a 4% survival rate with no treatment. These findings and a later study⁴⁰ in which r-metHuG-CSF was administered for a longer period suggest that G-CSF may act synergistically with antibiotics in preventing GBS sepsis. The myeloid marrow reserve is decreased in newborn rats compared with adults, as is also true in humans. Our patient had an unusual susceptibility to GBS, developing three episodes of sepsis with the same serotype prior to G-CSF therapy. Although ours is the only reported case, to our knowledge, of a premature infant treated with G-CSF, this cytokine may be useful in treating or preventing GBS sepsis in other infants who are not so severely neutropenic.

This case suggests that G-CSF may be used safely and effectively to treat premature infants with neonatal neutropenia, and a clinical trial using r-met HuG-CSF for neonatal neutropenia associated with sepsis is warranted. Although neonatal neutropenia is usually self-limited, it may contribute to a large number of infant deaths and morbidity when other risk factors, such as extreme prematurity or the need for assisted ventilation, are present.^{1,4,5} Our patient, unlike those previously described with Kostmann's syndrome and cyclic neutropenia, was able to discontinue r-met HuG-CSF treatment after 7 months and maintain a stable ANC. His lungs and immune system had also matured by the time the drug therapy was discontinued, thus making him much more resistant to the usual childhood illnesses.

To our knowledge, this is the first reported case of using r-metHuG-CSF as a temporary measure to treat the self-limited but often lethal neutropenia occurring in infants. The r-metHuG-CSF caused the neutropenia to resolve within 24 hours, produced no significant side effects, and could be discontinued after 7 months. Further studies on the use of this cytokine to treat neutropenia and septicemia in these highly vulnerable infants is warranted.

The authors thank Jeffrey Smith, MD, who performed the flow cytometry assays for the C3bi receptor on neutrophils; C. T. Barrett, MD, who brought this infant to our attention; Roger Kobayashi, MD, who assisted in the immunologic evaluation; and the other physicians and nurses who helped us collect data.

We also express our appreciation to Michelle Edenfeld for her secretarial expertise and to E. R. Stiehm, MD, for his editorial assistance.

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Predictors of Neurodevelopmental Outcome Following Bronchopulmonary Dysplasia

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● In infants with bronchopulmonary dysplasia, the influence of the severity of their pulmonary disease on neurodevelopmental outcome is unknown. Neurodevelopmental outcomes at a mean age of 36 months were assessed in 27 premature subjects who had bronchopulmonary dysplasia. Subjects had a mean birth weight of 940 g (range, 540 to 1690 g) and a mean gestational age of 27 weeks (range, 25 to 31 weeks). The duration of mechanical ventilation ranged from 22 to 128 days, and the duration of requirement of supplemental oxygen ranged from 34 to 1033 days. No significant correlations were found between duration of mechanical ventilation or oxygen therapy and overall neurodevelopmental outcome. In contrast, cranial ultrasound findings of intracranial hemorrhage and/or periventricular echodensity related specifically to poorer cognitive outcome. By age 3 years, severity of bronchopulmonary dysplasia is not a sufficient predictor of neurodevelopmental outcome. Intracranial hemorrhage and periventricular echodensity continue to be important predictors.

(AJDC. 1991;145:813-817)

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disease that often affects very premature infants during recovery from respiratory distress syndrome (RDS). The reported incidence of BPD varies between 5% and 70% depending on investigators' varying diagnostic criteria.¹⁻⁷ Very premature infants are known to be at increased risk of poor neurodevelopmental outcome, but it is not known whether the severity of pulmonary disease in infancy further increases this risk. Outcome investigations of survivors of RDS and BPD provide differing conclusions as to the neurodevelopmental performance of these populations.⁸⁻¹⁰ Some studies have shown that RDS and BPD are less important than birth weight, perinatal asphyxia, and other perinatal and neonatal events in predicting developmental outcome.¹¹⁻¹⁵ However, other studies have reported that severity of BPD is a more important predictor of developmental performance than

birth weight, gestational age,^{16,17} or intracranial hemorrhage (ICH).¹⁸

This report describes the neurodevelopmental outcomes at age 2 to 4 years of low-birth-weight, premature infants who experienced varying degrees of BPD. We investigated the hypothesis that there is a direct correlation between the severity of BPD as measured by the duration of mechanical ventilation and oxygen therapy and the risk of suboptimal neurodevelopmental outcome. The developmental sequelae of ICH and periventricular echodensity (PVE)/periventricular leukomalacia as identified on cranial ultrasound studies were also compared.

SUBJECTS AND METHODS

For purposes of this investigation, BPD was defined as the chronic pulmonary disease that develops in premature infants with RDS who require 30 or more days of supplemental oxygen therapy and who have abnormal chest roentgenographic findings after age 30 days. All study subjects were diagnosed using this definition of BPD by the attending neonatologist and radiologist who cared for them in the University of Washington (Seattle) Neonatal Intensive Care Unit. The clinical care of patients with BPD has been previously summarized.^{19,20} Ventilator pressure, rate, and fraction of inspired oxygen (F_{IO_2}) were altered in attempts to keep P_{aO_2} between 55 and 70 mm Hg, and arterial pH between 7.30 and 7.40. Pulse oximetry was used frequently to monitor arterial hemoglobin oxygen saturation to keep saturation between 90% and 94%. Alterations in ventilator settings were individualized for each patient. Diuretics, bronchodilators, sedatives, and steroids were used as clinically indicated.

The study population consisted of 27 infants born between January 1, 1984, and December 31, 1985, who met the described BPD criteria and were followed up longitudinally for 2 years or longer. Infants with congenital anomalies were excluded from study recruitment.

The 27 study subjects included 16 female and 11 male infants; 25 were white and two were Hispanic. The mean birth weight for the study population was 940 g (range, 540 to 1690 g), and the mean gestational age was 27 weeks (range, 25 to 31 weeks). The mean length of hospitalization was 97 days (range, 48 to 198 days). Study subjects were mechanically ventilated for a mean of 46 days (range, 22 to 128 days), and the mean total duration of oxygen therapy was 140 days (range, 34 to 1033 days).

All 27 study subjects were followed up longitudinally in the University of Washington High-Risk Infant Follow-up Program to a mean age at final evaluation of 36 months (range, 24 to 48 months). A developmental pediatrician performed a complete physical and neurodevelopmental examination of each child.

Accepted for publication February 13, 1991.

From the University of Washington School of Medicine, Seattle.

Presented in part at the annual meeting of the Western Society for Pediatric Research, Carmel, Calif, February 7, 1989.

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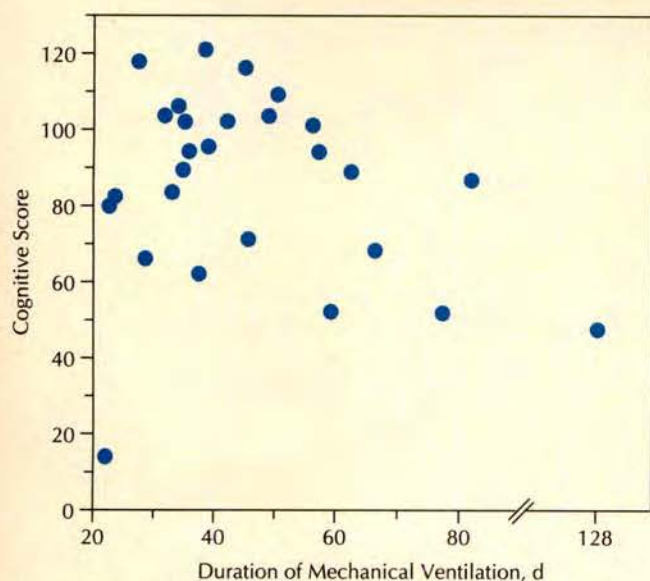


Fig 1.—Relationship between cognitive score and the duration of mechanical ventilation.

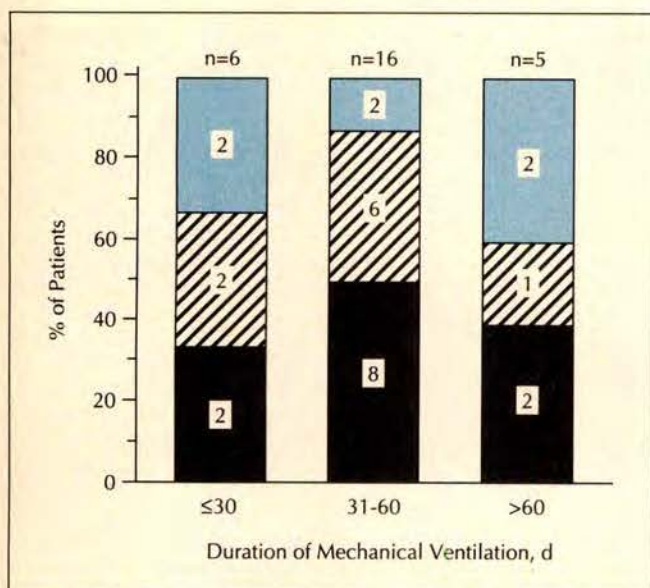


Fig 2.—Relationship between overall neurodevelopmental outcome and the duration of mechanical ventilation. Solid area represents patients with normal neurodevelopmental outcome; hatched area, those with minor abnormalities; and shaded area, those with major abnormalities.

Each child was evaluated by a clinical psychologist using the Bayley Scales of Infant Development, the Stanford-Binet Intelligence Scale, or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). The test administered depended on the age and developmental abilities of the subject. Both neurodevelopmental and psychological evaluations were performed using the child's conceptual age (chronologic age corrected for prematurity).

For data analysis purposes, the Bayley Mental Developmental Index, Stanford-Binet IQ, and WPPSI Full Scale IQ scores were combined to generate a "cognitive score" that describes the cognitive outcome of the group as a whole. Because these tests have similar psychometric properties with a standard mean of 100 and an SD of 15 or 16, it is acceptable to combine the scores for reporting purposes. We further combined the standardized test outcomes with findings from the neurodevelopmental examina-

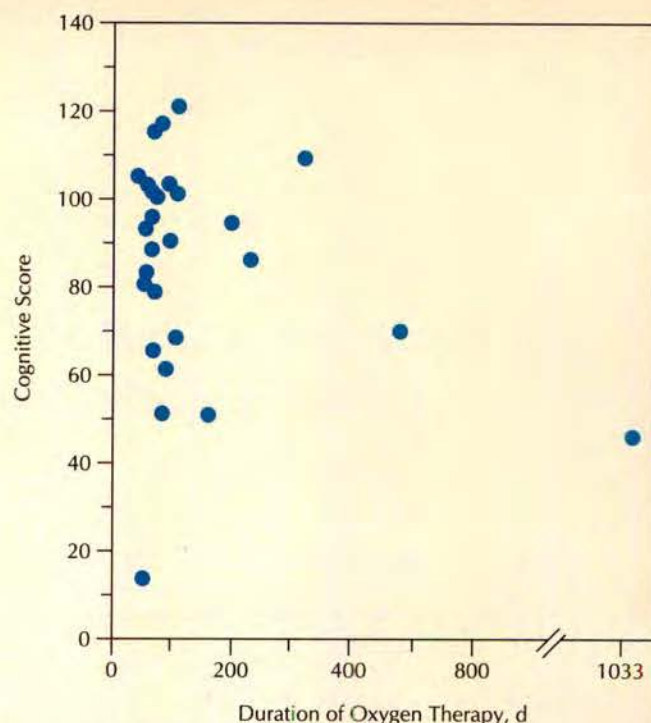


Fig 3.—Relationship between cognitive score and the duration of oxygen therapy.

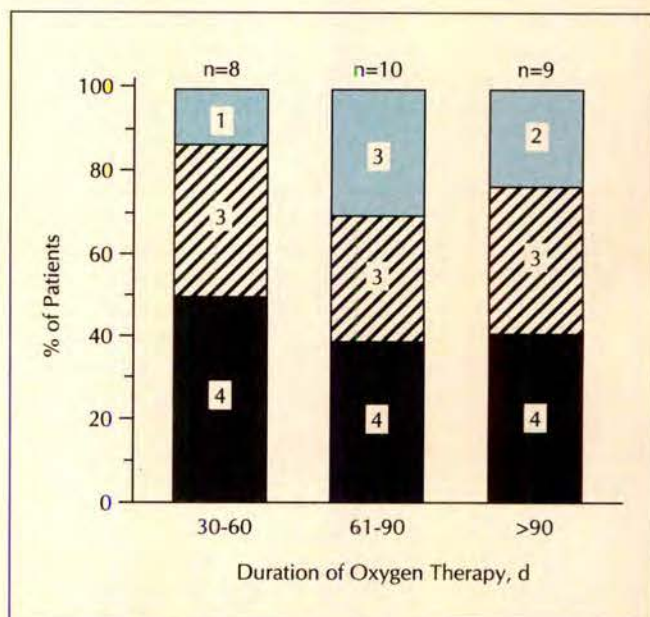


Fig 4.—Relationship of overall neurodevelopmental outcome and the duration of oxygen therapy. Solid area represents patients with normal neurodevelopmental outcome; hatched area, those with minor abnormalities; and shaded area, those with major abnormalities.

tion to produce an overall summary of neurodevelopmental outcome. Overall neurodevelopmental outcome was categorized as being normal (normal neuromotor and developmental performance), demonstrating minor abnormalities (mild disturbances of muscle tone, coordination, or motor milestones, and/or borderline cognitive function as reflected by a standardized psychometric assessment between 1 and 2 SDs below the mean), or demonstrating major abnormalities (diagnosed cerebral palsy or mental retardation as reflected by a standardized psychometric

Relationship of Overall Neurodevelopmental Outcome and Severity of Intracranial Hemorrhage (ICH) and Periventricular Echodensity (PVE)					
Grades of ICH/PVE	No. of Patients	Mean Cognitive Score	Overall Neurodevelopmental Outcome, No. (%)		
			Normal	Minor Abnormalities	Major Abnormalities
0/0	8	95	5 (63)	3 (37)	0
I-II/1,2	10	91	7 (70)	1 (10)	2 (20)
III-IV/3	9	70	0	5 (56)	4 (44)

assessment at 2 or more SDs below the mean).

All 27 study subjects underwent at least one cranial ultrasound examination during the neonatal period. Examinations were performed at the bedside with a commercially available, mechanical real-time sector scanner with a 7.5-MHz, medium internal-focused transducer. Scans were typically performed during the first week of life (most between age 2 and 5 days), second week of life (most between age 8 and 12 days), and at least once more beyond age 2 weeks (most between age 2 and 6 weeks). Thus, most subjects underwent three periodic cranial ultrasonographic examinations, with some subjects additionally examined with ultrasound and/or computed tomography at the discretion of the attending neonatologist. These ultrasound scans were reviewed for evidence of ICH and PVE. Intracranial hemorrhage was graded using a modification of the system of Papile et al²¹ as follows: grade 0, no evidence of ICH; grade I, subependymal hemorrhage only; grade II, intraventricular hemorrhage; grade III, intraventricular hemorrhage with ventriculomegaly; and grade IV, intraparenchymal hemorrhage. Periventricular echodensity was graded on a numerical scale of 0 to 3, with 0 indicating absolutely no echodensities, 1 and 2 indicating increasing degrees of observed echodensities without cysts, and 3 indicating cystic formation. For purposes of this study, the highest grades of both ICH and PVE coded on any scan were used in the data analysis.

Data analyses were performed with the assistance of the Data Management Core of the University of Washington's Child Development and Mental Retardation Center. Statistical methods included analysis of variance, linear regression, and χ^2 tests. $P \leq .05$ was considered significant.

RESULTS

Six of the 27 study subjects had their cognitive development assessed by means of the Bayley Mental Developmental Index. The mean mental developmental index for this subgroup was 78 (range, 14 to 121). Nineteen subjects were able to be assessed with the Stanford-Binet Intelligence Scale; the mean IQ of this subgroup was 86 (range, 52 to 117). Two subjects completed the Wechsler Preschool and Primary Scale of Intelligence and were found to have IQ scores of 101 and 103. The mean cognitive score for the entire cohort was 85 (range, 14 to 121). Twelve (44.4%) of the 27 study subjects were determined to have normal overall neurodevelopmental outcome, nine (33.3%) demonstrated minor abnormalities, and six (22.2%) were found to have major abnormalities.

Duration of mechanical ventilation was not significantly related to cognitive score in this group of BPD survivors ($P = .09$). Figure 1 demonstrates the distribution for all 27 subjects comparing cognitive score by duration of mechanical ventilation. Likewise, duration of mechanical ventilation was not significantly correlated with overall neurodevelopmental outcome ($P = .08$, Fig 2). Two subjects in each of the three categories of duration of mechanical ventilation demonstrated major abnormalities.

Similarly, duration of oxygen therapy failed to reliably predict cognitive score ($P = .07$), as demonstrated by the data point distribution in Fig 3 ($P = .09$) in overall neurodevelopmental outcome between subjects in three categories of duration of oxygen therapy. There were the same number of subjects with normal outcome and with minor abnormalities in each of the three duration categories.

The Table summarizes the mean cognitive score and overall neurodevelopmental outcome for three subject subgroups divided by severity of ICH and PVE. In the subgroup of eight subjects with entirely normal cranial ultrasound readings, there were no subjects with major neurodevelopmental abnormalities. Of the 10 subjects with grade I or II ICH or grade 1 or 2 PVE or both, seven (70%) had normal neurodevelopmental outcome. In contrast, the subgroup of nine subjects with grade III or IV ICH, cystic grade 3 PVE, or both had no subjects with normal neurodevelopment. By analysis of variance, we found that increased severity of ICH and PVE is associated with worse neurodevelopmental outcome ($P = .002$). Mean cognitive scores were within the average range for the two study subgroups with normal or less severe cranial ultrasound findings in contrast to the mean cognitive score of 70 for the nine subjects with the most abnormal neuroimaging results ($P = .022$).

COMMENT

The present study assessed the cognitive and neuromotor outcomes at 2 to 4 years' corrected age in a cohort of children born prematurely who required extended mechanical ventilation for neonatal RDS and 30 or more days of supplemental oxygen therapy. We were unable to demonstrate a clear and consistent correlation between the severity of BPD and suboptimal neurodevelopmental outcome. No significant relationships were found in this cohort between the duration of mechanical ventilation or oxygen therapy and cognitive performance or overall neurodevelopmental outcome. While nonsignificant outcome trends were apparent for duration of both mechanical ventilation and also oxygen administration, one outlier subject (ie, 128 days of mechanical ventilation and 1033 days of oxygen therapy) exerted an unusually large influence on the two linear regressions. Exclusion of this one subject from the data analyses would have substantially diminished these suggestive trends.

These data support our previous observations that other factors related to low birth weight and prematurity may be more important contributors to eventual outcome than pulmonary disease.¹³ This has also been the experience of many other investigators. Fisch et al¹¹ reported convergence to similar neurodevelopmental performance after the first year of life in low-birth-weight RDS survivors and control subjects without RDS matched for birth weight. More recently, Piekkala et al¹⁴ and Ludman et al¹⁵ have described the relative lack of impact of uncomplicated RDS on neurodevelopmental outcome at 2 and 4 years of age, respectively. In the study by Piekkala et al,¹⁴ the factors most predictive of abnormal long-term development were ICH, hypoxic-ischemic encephalopathy, and very low birth weight. However, the majority of infants in these

studies did not meet BPD criteria and the findings may not be applicable to those infants with more severe and prolonged pulmonary disease.

Markestad and Fitzhardinge¹² found perinatal/neonatal factors (eg, birth asphyxia, metabolic acidosis, intraventricular hemorrhage) to be better predictors of developmental outcome than the presence or absence of BPD in 20 premature subjects followed up to 2 years of age. In contrast, Meisels et al¹⁶ reported that 17 survivors of BPD performed significantly worse on developmental measures in the second year of life than their 20 counterparts with less severe RDS. They also found severity of BPD to be a better predictor of developmental performance than birth weight or gestational age. In a study of 159 low-birth-weight infants, Bozynski et al¹⁸ contrasted the effects on development of prolonged mechanical ventilation for BPD with the presence of ICH. The infants who required prolonged mechanical ventilation had uniformly poor performance on developmental scales at 4, 8, 12, and 18 months' corrected age, whereas ICH did not have consistent detrimental effects on developmental scores. These authors concluded that mechanical ventilation for more than 21 days is a powerful predictor of developmental delay up to 18 months of age, while ICH is not.

The major difference between this study and previous BPD outcome investigations is the length of follow-up. While the major recent reports in this area have described 18 to 24 months' performance, we are reporting neurodevelopmental status beyond the age at which these studies conclude, ie, from 24 through 48 months. This older follow-up age (mean, 36 months) provides two distinct study advantages. On the one hand, it allows for more comprehensive reliable developmental assessment with instruments of greater long-term predictive validity. Even more important, for recovering, medically fragile, very premature infants, it allows for an adequate period of developmental "catch-up" to have occurred before making outcome conclusions and prognostications. Borderline, mild, and even moderate developmental delays in the first 2 years of life may substantially improve and even disappear over time coincident with steady, gradual improvement in the child's health status. Of course, the more severe developmental retardation that has been reported to occur in those few infants with extremely prolonged hospitalization and assisted ventilatory requirements (ie, 6 months or longer) would be anticipated to be of a more permanent nature.²⁰

While the influence of neonatal pulmonary disease on neurodevelopmental outcome appears to diminish over time, we found a persistent, deleterious impact of common intracranial complications (ie, ICH and PVE) on ultimate long-term performance. Again, one major explanation for the contrasting interpretations of Bozynski et al¹⁸ concerning the relative developmental importance of respiratory vs certain intracranial events is their shorter follow-up. As infants slowly recover from chronic pulmonary disease, the residual and permanent neurodevelopmental effects of perinatal/neonatal intracranial complications may become more apparent.

It is encouraging that the majority of our study subjects were free of major abnormalities. Nevertheless, the observation that less than one half of this cohort could be categorized as having normal overall neurodevelopmental outcome as well as the relatively high prevalence of minor

abnormalities mandates caution in terms of predicting school-age function. In time, these less severe but functionally disabling conditions are likely to be encountered with increased frequency in this vulnerable population.

This study suffers from a somewhat small BPD cohort and the lack of a matched premature contrast group without neonatal pulmonary disease. However, BPD was consistently defined, and the investigation's primary purpose was to identify the neurodevelopmental predictive utility of neonatal respiratory and intracranial complications, rather than to describe long-term outcome in BPD in general. Sociodemographic environmental variables not measured by this study also influence outcome. With these cautions in mind, our follow-up of premature BPD survivors into the preschool years confirms the complex, multifactorial nature of determining future neurodevelopmental performance. While severe BPD clearly constitutes an important risk factor for permanent central nervous system dysfunction, follow-up indicates that this risk is not a simple direct relationship and that other interactive variables may eventually prove to be more important.

This study was supported in part by a grant from the Washington Association for Retarded Citizens Research Trust Fund.

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BOOK REVIEW

The H. L. Mencken Baby Book

By Howard Markel and Frank A. Oski,
194 pp, \$20, Philadelphia, Pa, Hanley
and Belfus Inc, 1990.

How's that again? A baby book by H. L. Mencken, the great Baltimore, Md, curmudgeon? An oxymoron for sure!

Amazing? Apparently not. In the summer of 1907, a physician, a magazine editor, and a reporter in Baltimore (Mencken) joined forces to prepare a series of magazine articles that culminated in a book entitled, *What You Ought to Know about Your Baby* (Butterick, 1910). The current volume, revised and updated, was prepared by Howard Markel, a pediatric intern in 1986 at The Johns Hopkins Hospital, Baltimore, and a Mencken aficionado, and Frank Oski, the chairman of Pediatrics at The Johns Hopkins University Medical School. The authors review the collaboration of Mencken, Leonard Hershberg (the physician), and Theodore Dreiser (the magazine editor), and include a

complete reproduction of the original text.

Both parts of the book are fascinating. Chapters discuss the newborn, nursing, bottle feeding, milk, food for growing children, schooling, and "catching diseases." Questions for mothers are included at the end of each chapter, along with the 1910 answers and current answers with up-to-date and appropriate information for parents.

Here are some sample quotations from Mencken:

Two considerations must be kept ever in mind in discussing the care of infants. One is the fact that silly superstitions, far from being confined to the slum mothers who give their babies beer and dress them in wadded flannels, are rampant to an astonishing degree among women otherwise intelligent and presumably sane (p 29).

Next to unwise feeding, as a source of infantile ills, comes over-coddling. Kissing the baby after it has been fed, for instance, is very likely to cause it to vomit, and vomiting is even more exhausting to a child than to an adult. The desire of all aunts, cousins, sisters, grandmothers, neighbors, parlor maids, cooks, seamstresses, and other members of the affectionate sex to hold the baby and kiss it,

and of all uncles, grandfathers and bachelor friends of its father to hoist it to the ceiling should be rigorously denied (p 33).

I sometimes think, indeed, that the degree of civilization of a community may be judged by the contents of its average family medicine chest. In the old days this chest bulged with herbs, barks, roots, soothing syrups, headache powders, lint salves, and ointments. Paregoric was in a place of honor, and behind it stood carboise of arnica and sweet spirits of nitre. In the future, I fancy, the medicine chest will be smaller and less horrifying. It will contain a box of aseptic cotton, a bottle of carbolic Vaseline, a bottle of castor oil, a hot water bag, and very little else (p 160).

Despite my initial incredulousness at the very existence of this book, Drs Markel and Oski have provided a delightful experience for all of us interested in children and good writing. Modern pediatricians and parents will clearly enjoy this unusual compilation of the progress of infant and child care in the 20th Century.

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University of Arizona
College of Medicine
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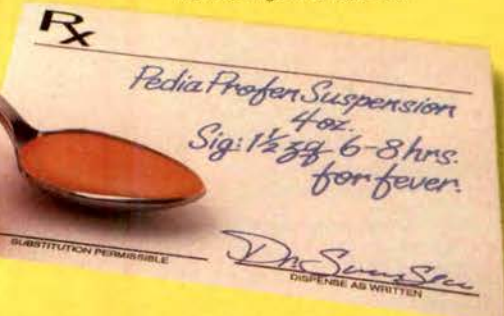
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1. Watson PD et al. Ibuprofen, acetaminophen, and placebo treatment of febrile children. *Clin Pharmacol Ther*: 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company.

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INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on PediaProfen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

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Radiological Case of the Month

Ahmed H. Al-Salem, FRCSI, FICS, Chris Grant, FRCS (Contributors);
Beverly P. Wood, MD (Section Editor)

A 4-month-old male infant was admitted to the hospital because of recurrent respiratory infections that started early in the neonatal period. He had been admitted to hospitals at ages 6 days, 50 days, and 3 months for treatment of respiratory infections. His physical examination revealed respiratory distress with decreased breath sounds in the left hemithorax. The cardiac examination results were normal. A chest radiograph was ob-

tained (Fig 1). Culture of tracheal aspirate yielded *Streptococcus pneumoniae*. The patient was treated with antibiotics and chest physiotherapy. Despite clinical improvement, there was no alteration in the chest radiographic findings. A computed tomographic scan of the chest (Fig 2), bronchoscopy, and bronchography (Fig 3) were performed. Bronchoscopy showed no inhaled foreign body.

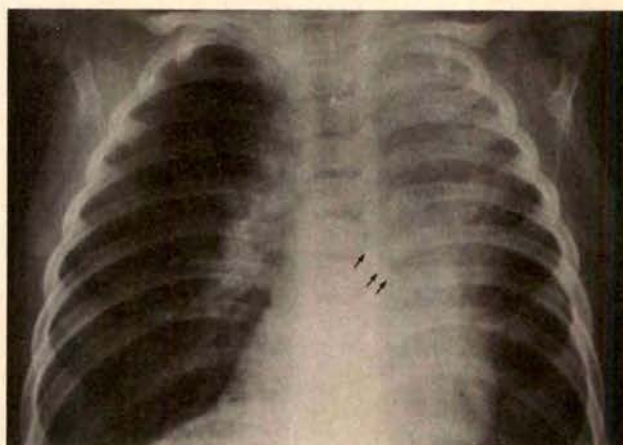


Figure 1.

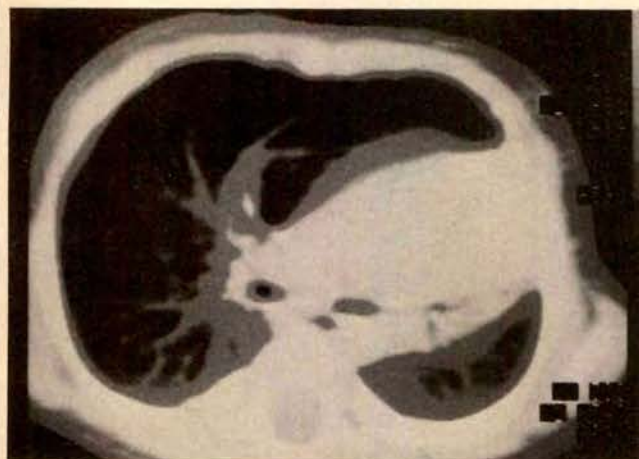


Figure 2.

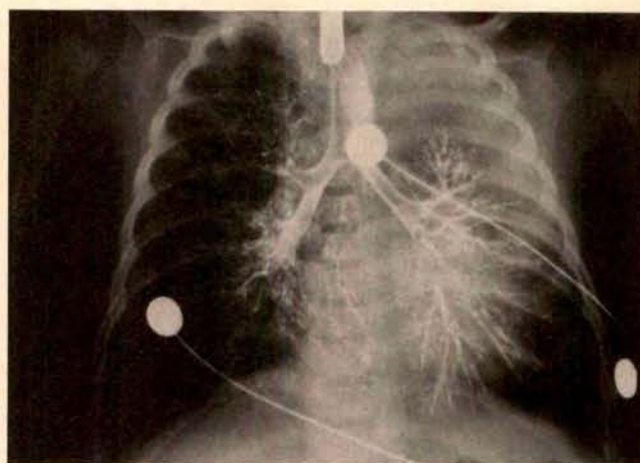


Figure 3.

Accepted for publication March 12, 1990.

Contributed from the Pediatric Surgery Division, Department of Surgery, King Fahd Hospital of the University, PO Box 2208, Al-Khobar 31952, Saudi Arabia.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Denouement and Discussion

Hypoplastic Left Upper Lobe

Fig 1.—Anteroposterior radiograph of the chest shows opacity in the left upper hemithorax, a shift of the mediastinum to the left, reflecting decreased lung volume on that side, and increased volume of the right lung. The left main-stem bronchus is low (arrows), and the pattern of density does not demonstrate the usual configuration of lobar atelectasis.

Fig 2.—Computed tomographic scan of the chest shows compensatory hyperinflation of the right upper lobe with midline herniation. The left hemithorax is small.

Fig 3.—Bronchogram shows visualization of the bronchial tree bilaterally. The upper lobe bronchi on the left are hypoplastic, and all bronchi are displaced downward. No bronchi communicate with the opacity in the left upper thorax.

At thoracotomy, the patient was found to have a markedly hypoplastic left upper lobe that was firm, consolidated, and had fibrinous pleural adhesions. The right lung was hyperexpanded. While dissection was carried out for a left upper lobectomy, the patient developed severe bradycardia and hypotension from reflex vagal stimulation. He was resuscitated and recovered, but soon developed another such episode. The procedure was postponed and the infant was admitted to the intensive care unit. Seven days later, he experienced a cardiac arrest and died.

In the development of the respiratory tract, interference with bronchial branching, pulmonary artery arborization, and subsequent development of the lung mesenchyme result in a wide spectrum of pulmonary malformations.^{1,2} Boyden³ has classified hypoplastic developmental anomalies of the lung into the following categories: (1) agenesis, in which there is complete absence of one or both lungs, without bronchial or pulmonary arterial supply or differentiated parenchymal tissue; (2) aplasia, in which a rudimentary bronchus ends in a blind pouch with no arterial supply or parenchymal development; and (3) hypoplasia, in which the bronchus is formed but is very small and ends

in a fleshy mass of undifferentiated lung mesenchyme.

Hypoplasia may involve the entire lung or a lobe. The most common association of pulmonary hypoplasia is with a congenital diaphragmatic hernia.⁴ Congenital hypoplasia also results from interference with the progressive development and arborization of the bronchiolar-acinar groups during the period of rapid growth in the third trimester of gestation.⁵ Acquired hypoplasia may result from severe infection, with extensive parenchymal involvement in infancy and inhibition of further development. When one lobe is hypoplastic, the patient may be asymptomatic, but common symptoms are those of recurrent respiratory infection. Although developmental defects of the lung are uncommon, awareness of the possibility is essential in prospective management.

Diagnosis by chest radiography is difficult because the appearance mimics some features of atelectasis. A computed tomographic scan of the chest is helpful in identifying hypoplasia of the thorax and hypoplastic or absent bronchi, also shown by bronchography (Fig 3). Bronchoscopy and computed tomography exclude possible extraluminal or intraluminal bronchial obstruction.

Treatment consists of antibiotics and chest physiotherapy for superimposed infection. An infected hypoplastic lobe may require resection since it lacks the usual intrinsic mechanisms for combating infection and stasis of secretions.

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Picture of the Month

Walter W. Tunnessen, Jr, MD (Contributor and Section Editor)



Figure 1.



Figure 2.



Figure 3.



Figure 4.



Figure 5.



Figure 6.

Accepted for publication January 3, 1991.
Contributed from the Children's Hospital of Philadelphia (Pa).
Reprint requests to Children's Hospital of Philadelphia, 34th St
and Civic Center Blvd, Philadelphia, PA 19104 (Dr Tunnessen).

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Tunnessen (Picture of the Month), The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104, or Dr Wood (Radiological Case of the Month), Department of Radiology, Children's Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Denouement and Discussion

Henoch-Schönlein Purpura

Fig 1.—Ecchymotic lesions.

Fig 2.—Petechial lesions.

Fig 3.—Targetoid lesions.

Figs 4 and 5.—Vesicular lesions.

Fig 6.—The elastic sock sign.

Manifestations

Henoch-Schönlein Purpura (HSP) is a systemic vasculitis of unknown cause. Involvement of the skin is the most characteristic feature of this disorder. The rash of HSP is described as purpuric and, classically, as demonstrating palpable purpura. The children pictured on the previous page all have HSP, but their skin involvements differ considerably in appearance. The variability in appearance of the rash associated with HSP may lead to confusion regarding the correct diagnosis unless associated features make other possibilities less likely.

Before the appearance of the purpura, the rash sometimes appears as erythematous maculopapules or as urticarial lesions. These lesions usually become purpuric and can be ecchymotic (Fig 1) or petechial (<3 mm, Fig 2). Occasionally, the lesions appear targetoid (Fig 3), but rarely become vesiculobullous (Figs 4 and 5). The elastic sock sign (Fig 6) is helpful in clinically separating the vasculitis of HSP from purpuric lesions associated with thrombocytopenia. The sign is created by linearly circumferential lesions corresponding to the top of the sock.

Another important feature of the rash of HSP is its acral distribution. The lesions primarily occur symmetrically over the buttocks and lower extremities. They are less commonly found on the upper extremities and face. The trunk is rarely involved.

The diagnosis of HSP is rarely made without the presence of the rash because the noncutaneous features may not be specific enough to warrant this diagnosis. In most cases, the rash precedes other features of the disease, but abdominal pain or arthralgia may precede the rash by up to 2 weeks.¹ Although the purpuric lesions fade over several days of bed rest, they commonly reappear when ambulation resumes.

Another curious cutaneous finding in HSP is the appearance of localized areas of subcutaneous swelling. The hands, feet, and scalp are the areas most often affected by

edema, but facial, periorbital, scrotal, and lumbar areas may also be affected. The edema is often painful.

Noncutaneous features of HSP may also include periarticular swelling, colicky abdominal pain with melena, guaiac-positive stools, hematemesis, and intussusception, nephritis, hypertension, orchitis, and encephalopathy. Nephritis occurs in 40% to 60% of children with HSP and is almost always present within the first 3 months after the onset of the illness.¹ There seems to be no correlation between the degree of nephritis and the severity of extrarenal manifestations.² The long-term morbidity of HSP is generally of renal origin, with an incidence of chronic renal disease of 6% to 38% at follow-up.³ A more recent study in an unselected population of children with HSP in Belfast, Ireland, found that 54 (20%) of 270 patients initially had evidence of renal disease, but only three (1.1%) demonstrated long-term morbidity.³ This is a much better prognosis than those of previous reports and may represent the lack of selection bias.

Treatment

The cause of HSP remains unclear, but it is believed to be a hypersensitivity reaction triggered by a variety of stimuli, including viral infections, insect bites, food allergies, vaccinations, and drug therapy. Most cases resolve spontaneously and last an average of 3.9 weeks (range, 3 days to 2 years).⁴

Histologic findings of leukocytoclastic vasculitis on skin biopsy are characteristic of HSP, and such findings may help recognition of the condition. The demonstration of immunoglobulin deposition, especially IgA in vessel walls by immunofluorescence, may also help confirm the diagnosis.⁵

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All classified advertising orders, correspondence and payments should be directed to: American Journal of Diseases of Children, P.O. Box 1510, Clearwater, Florida 34617. Our telephone numbers are: 800-237-9851; 813-443-7666. Please do not send classified ads, payments or related correspondence to the AMA headquarters in Chicago. This causes needless delay.

Inquiries about "BOX NUMBER" advertisements: All replies must be in writing and must cite the box number in the ad. Example: Box _____, c/o AJDC, P.O. Box 1510, Clearwater, Florida 34617. We are not permitted to divulge the identity of advertisers who wish their mail sent in care of American Journal of Diseases of Children.

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Cost per word	\$1.85	\$1.70
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One-half page	809	704
One-third page	638	554
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Professional Opportunities

BC/BE PEDIATRICIAN to join two BC private practice pediatricians in upstate New York, Thousand Islands region. Affiliation leading to partnership. Level II NICU, cystic fibrosis center. Stimulating practice with an on-call arrangement with other pediatricians, excellent recreational facilities and schools in a thriving small city with many cultural advantages. A good place to raise children, too. Contact: R.G. Perliaccante, MD, 199 Pratt Street, Watertown, NY 13601.

NEONATOLOGIST to join five-member BC/BE group in a Level III perinatal center with academic affiliation. For further information, contact: B.T. Bloom, MD, 550 North Hillside, Wichita, KS 67214. (316) 688-2360.

THIRD PEDIATRICIAN - BRAINERD, MINNESOTA: Join two pediatricians of 22 multi-specialty clinic. No set-up cost. Two hours from Minneapolis. Beautiful lakes and trees; ideal for families. Call collect/write: Curt Nielsen, (218) 828-7105 or (218) 829-4901; Brainerd Medical Center, P.O. Box 524, Brainerd, MN 56401.

FOUR CONGENIAL PEDIATRICIANS seek fifth pediatrician for rapidly expanding practice. This practice is located in an affluent growing community in northern California within a two-hour access to San Francisco and Lake Tahoe. Guaranteed salary for two years with partnership options at the end of the two-year period. Write or call: P.O. Box 787, Lodi, CA 95240. (209) 369-7493.

ADIRONDACK FOOTHILLS opportunity! Modern 124-bed hospital in upstate New York is offering a generous financial package for BC/BE pediatrician interested in establishing a private practice with excellent coverage arrangements. Guaranteed income, start-up funds, malpractice insurance, cash-flow assistance. Located in a family-oriented community with year-round recreation, excellent schools, and beautiful surroundings. Contact: Lyn I. Kucij, Director of Marketing and Development, Nathan Littauer Hospital, 99 East State Street, Gloversville, NY 12078. (518) 773-5504. Please call collect.

IMMEDIATE OPENING for BC/BE pediatrician to associate with well-established, rapidly growing, 32-MD multi-specialty group. Located in the San Francisco Bay area in a growing community serving 170,000. Patients include both fee-for-service and prepaid health plan. Attractive compensation and benefits. Malpractice provided. California license required. Send CV to: Bart Bona, Administrator, Fairfield Medical Group, Caller Box 4020, Fairfield, CA 94533-0410. (707) 426-3911.

DELAWARE - General Pediatrician: The Nemours Foundation will develop several new general pediatric clinics in southern Delaware. These privately funded and administered clinics will offer a unique opportunity to serve a growing pediatric population in a coordinated statewide health care system. They will be located in underserved semi-rural areas and will consist of a general pediatrician and a pediatric nurse practitioner working together as a team in a modern computerized office setting. Tertiary care will be provided by the Alfred I. duPont Institute in Wilmington, Delaware. These clinics will be minutes from the Atlantic beaches and the Chesapeake Bay. The major metropolitan areas of Washington, Baltimore, Philadelphia and Wilmington will be within a two hour drive. If you have a desire to serve children in genuine need of good medical care, reply to the address below. Salary and fringes are distinctly above average. Reply to: The Alfred I. duPont Institute, Thomas P. Ferry, Administrator, P.O. Box 269, Wilmington, DE 19899. Telephone: (302) 651-4000.

Professional Opportunities

MAINE: Immediate opportunity for a fourth BC/BE pediatrician with general and/or subspecialty interests to join a multi-specialty group affiliated with a 250-bed regional referral hospital. Enjoy the professional challenge offered in a sophisticated medical community along with the wonderful recreational opportunities and quality of life in Maine. Please send CV to: Richard Marsh, MD, 76 High Street, Suite 203, Lewiston, ME 04240. Or call: (207) 795-2389 and ask for Shannon Tamminen.

TWO PEDIATRICIANS seeking third BC/BE pediatrician to join two site, growing practice. Ideal all season recreational area. Ideal site for young family. Please contact: Tahoe City Pediatrics, P.O. Box 6959, Tahoe City, CA 95730.

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Generous Salary and Benefits
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Community Oriented Primary Care
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We've got it all!

Send CV to: James Goetz, MD, Medical Director,
Oak Orchard Community Health Center
80 West Avenue, Brockport, New York, 14420

ROCHESTER, NEW YORK - Opportunity for a general pediatrician to develop their practice as part of the Rochester Medical Group pediatric department. Rochester Medical Group is a multi-specialty group practice which cares for fee-for-service as well as prepaid patients. In addition to full-time position, willing to consider part-time or job-share opportunities. Subspecialty interests possible. University affiliation encouraged. Competitive salary and benefits. Located in attractive metropolitan area with many cultural and recreational advantages. Send resume or call: Rochester Medical Group, P.C. Attention: James Tobin, MD, 800 Carter Street, Rochester, NY 14621. (716) 338-1400. EOE, M/F.

NEONATOLOGIST: Marshfield Clinic, a 350 physician multi-specialty private group practice in central Wisconsin, is seeking a fourth BC/BE neonatologist to join its 20-member pediatric department. Adjacent 524-bed acute care teaching hospital includes a 24-bed, Level III Neonatal Unit. Full pediatric support subspecialties are available on-site. Pediatric Residency Program, University of Wisconsin Medical School affiliation, Medical Research Foundation and large regional referral base contribute to a very stimulating environment. Marshfield, a community of 20,000, was recently designated as "one of the best small cities in the Midwest." Send curriculum vitae plus the names of several references to: James C. Opitz, MD, Marshfield Clinic, 1000 North Oak Avenue, Marshfield, WI 54449. Or call collect: (715) 387-5016.

Professional Opportunities

UPSTATE NEW YORK – BC/BE pediatrician to join well established pediatric group. Early partnership. Nice, safe community. Call or CV to: Felipe Canizares, MD, 421 Main Street, Oneida, NY 13421. (315) 363-2350.

NORTHWESTERN PENNSYLVANIA – BC pediatrician seeks second pediatrician (BC/BE) to be on team of well-established, quality care multi-specialty group of eighteen physicians in town of 15,000. Exceptional hospital with 12-bed pediatric unit and Level I nursery serving 600 deliveries a year. Excellent living and working environment. Attractive salary and benefits. Send CV: Box #121, c/o AJDC.

WASHINGTON – Established, five full-time, one part-time pediatric group seeking full-time BC/BE pediatrician. Beautiful, rapidly growing community in midst of mountains and water, one hour from Seattle. Local hospital and nearby children's hospitals. Opportunity to practice a wide range of pediatric skills. Competitive salary; early partnership. Reply with cover letter and CV to: Medical Director, Kitsap Children's Clinic, 2625 Wheaton Way, Suite A, Bremerton, WA 98310. (206) 479-1651.

OPPORTUNITY FOR EXCELLENT practice in high desert area of New Mexico. Our southwest paradise cares about its children and their physicians. Call coverage and financial assistance available. Call Jo Grimm, (800) 638-6942

SOUTHERN CALIFORNIA – Established pediatric practice available. Prestige location, \$250,000 gross and growing. Reply to: V. Hemingway, P.O. Box 2205, Orange, CA 92669.

PENNSYLVANIA – Pediatrician needed. \$130,000 net plus M/P insurance, full benefits, new office and operating expenses provided. One in four call. Built-in referrals. Population 200,000. Must be a dynamic self-starter interested in clinical practice development, recruiting pediatricians, development of pediatric services clinic. Must be board-certified. Call or send CV to: Perry Robinson, Cejka & Co., 222 South Central, Suite 700, St. Louis, MO 63105. (800) 765-3055.

Professional Opportunities

HAWAII – PEDIATRICIAN: Opportunity with an established and growing multi-specialty group practice. Competitive compensation and excellent benefits. If working with congenial associates in a quality oriented environment is for you, why not consider relocating to the Hawaiian Islands? Send CV or call: Rex Couch, MD, Medical Director, Kauai Medical Group, Inc., 3420-B Kuhio Highway, Lihue, HI 96766. (808) 246-1624.

DYNAMIC, HIGH GROWTH multi-specialty community health center with twenty-six providers has an opening for an additional pediatrician. Also seeking physician's assistant to supervise new adult correctional facility. Excellent compensation. Paid malpractice. CV to: John F. Frana, Executive Director, Crusader Clinic, 120 Tay Street, Rockford, IL 61102. (815) 968-0286. EOE.

AUSTIN, TEXAS – Seeking general pediatrician BE/BC for full time position. Call or write: Mrudula Deshpande, MD, 13740 Research, V-1, Austin, TX 78750. (512) 250-0406.

PEDIATRICS/ARKANSAS – Well established pediatric group seeks fourth member in scenic community of 60,000. Located forty miles south of Little Rock, Arkansas. Affiliation with 400-bed regional medical center. Competitive financial package offered. Send CV to: Andrew Johns, Physician Services of America, Suite 250, 2000 Warrington Way, Louisville, KY 40222. Or call: (800) 626-1857.

BC/BE PEDIATRICIAN needed July 1, 1991 for full-time hospital-based position covering Level I-II Nursery and pediatric emergency patients. Suburban St. Louis community hospital in affiliation with tertiary-care pediatric center with academic opportunities available. Competitive salary, excellent benefits, time to pursue outside interests, and no off-site call. Send curriculum vitae to: Richard Barry, MD, St. Louis University Department of Pediatrics, Cardinal Glennon Children's Hospital, 1465 South Grand Boulevard, St. Louis, MO 63104. (314) 577-5360. M/F/H/V. EEO employer. Women and minorities encouraged to apply.

Professional Opportunities

LARGE MULTI-SPECIALTY GROUP in northern Virginia area needs bilingual (Spanish) pediatrician to replace retiring physician of forty years. Send CV to: Medical Director, Falls Church Medical Center, 6060 Arlington Boulevard, Falls Church, VA 22044.

OHIO – Outstanding pediatric opportunities exist for BE/BC pediatricians to join successful pediatric groups and partnerships in the affluent suburbs of Toledo, Ohio. These high-profile, growth-oriented practices offer a variety and diversity of styles – from general pediatrics to specialized pediatrics. All are located in spacious, modern, and fully equipped facilities. Excellent call coverage readily available. These thriving practices are affiliated with the prestigious Toledo Hospital, a 784-bed medical center that has seven neonatologists and sixty pediatric beds. All pediatric subspecialties are available, including four pediatric intensivists/pulmonologists. Each pediatric group offers a competitive financial package. For comprehensive details, send CV to: Andrew Johns, Physician Services of America, Suite 250, 2000 Warrington Way, Louisville, KY 40222. Or call: (800) 626-1857, Extension 237.

PEDIATRICIANS – MARYLAND: BC/BE with neonatal skills to provide ongoing coverage, nights and weekends, in a regional, tertiary level NICU. Responsibilities include supervision of pediatric residents and hands-on care. Send inquiries to: Howard J. Birenbaum, MD, St. Agnes Hospital, 900 Caton Avenue, Baltimore, MD 21229. Or call: (301) 368-2504.

PEDIATRICIAN – SEATTLE: Outstanding pediatric practice seeking an associate. Busy practice, affiliated with excellent 300-bed general hospital. Must be board-certified or board-eligible. Contact: Richard G. Wedig, Highline Hospital, 12844 Military Road South, Seattle, WA 98168. (206) 248-4561.

NEED A DOCTOR? For the most comprehensive coverage to specific specialties and select subspecialties, put your recruitment ad in an AMA specialty journal. We target your ad to the physician you want. To schedule your ad call our "Classified Advertising" office: National (800) 237-9851; Local (813) 443-7666.

NORTH CAROLINA – Excellent pediatric partnership available in Charlotte. One in three call. No buy-in. Competitive guaranteed salary. Well-established, high profile practice affiliated with prestigious multi-specialty clinic. For further details send CV to: Andrew Johns, Physician Services of America, Suite 250, 2000 Warrington Way, Louisville, KY 40222. Or call: (800) 626-1857, Extension 237.

SAVANNAH, GEORGIA – General pediatrician wanted to join four-member group. Growing practices include a satellite office. Guaranteed salary, productivity incentive and early buy-in offered. Personal and professional life in Savannah can be very rewarding. Contact: William Hutcheson, MD, (912) 354-5814.

PHILADELPHIA – Two pediatricians seeking BE/BC third for growing practice in southwest Philadelphia. Full partnership opportunity after two years. Send CV to: Fredric Nelson, MD, 2801 Island Avenue, Philadelphia, PA 19153.

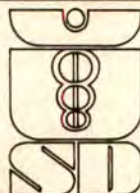
BC/BE PEDIATRICIAN NEEDED. Busy office practice. Guaranteed salary, benefits. Mountain local. CV to: Mike McCraley, Ogden Clinic, 4650 Harrison Boulevard, Ogden, UT 84403. (801) 479-4621.

Positions Available

INTERMOUNTAIN HEALTH CARE, One of the nation's largest not-for-profit health care systems with 24 hospitals, has practice opportunities available for BE/BC pediatricians in the scenic Intermountain West. Situations range from rural to urban areas and from employment to private practice positions. Work within a premiere health care system and live in beautiful and affordable mountain states with four-season recreational opportunities including skiing, backpacking, hunting, and sightseeing in numerous national parks and forests. Send CV to: Betty Anderson, IHC Physician Services, P.O. Box 57010, Murray, UT 84157-0010. Or call toll-free: (800) 888-3134, Extension 4515.

Pediatric Subspecialists

**Cardiology
Pulmonology
Hematology/Oncology
Neurology
Surgery
Neonatology**



The University of South Dakota School of Medicine currently has openings for BE/BC pediatric subspecialties.

These are full-time academic positions ideally suited for the clinician scholar who wishes to develop and guide a program which will have a significant impact on the health care of children. Although our program is heavily slanted toward medical student education and patient care, the department encourages and provides ample resources for clinical and laboratory research.

Sioux Falls, included in David Frankes' book, America's Fifty Safest Cities, has a strong economic base, growing population and a progressive educational system. South Dakota's four season climate welcomes endless recreational activities year-round.

Competitive financial packages offered. EOE/AEE.

Send CV or call:
Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

Practices Available

SOUTH CAROLINA – Growing pediatric practice in growth area of state. Low overhead with physician netting about \$90,000. Close to dynamic Charleston. Contact: Gary Schaub, P.O. Box 69155, Portland, OR 97201. (503) 223-4357.

Directors Wanted

NEONATOLOGIST: Director for a 6.5 member community section within the Division of Neonatology of the State University of New York at Buffalo. Using nurse practitioners, the section will provide coverage for a 12-bed Level II Nursery and two Level I Nurseries with a total of 8,500 deliveries. Its members will also rotate through the Level III Nursery and teach fellows, residents and nurse practitioners. The Division of Neonatology currently has ten faculty members and covers a 75-bed Level III Nursery. It conducts NIH sponsored laboratory research and clinical research including six years of experience with surfactant therapy. Contact: Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. (716) 878-7673. Affirmative action/equal opportunity employers.

Fellowships

NEONATAL-PERINATAL Medicine Fellowship – First and second-year opening for August 1, 1991. Balanced university program with broad research base. The fellowship provides ample opportunity for clinical and laboratory investigation and emphasizes preparation for a career in academic medicine. Interested candidates should contact: Karen D. Hendricks-Munoz, MD, MPH, Director, Neonatal Program Department of Pediatrics, New York University Medical Center, New York, NY 10016. (212) 263-7477. An affirmative action/equal opportunity employer, encourages minority and women candidates' application.

Faculty Positions

AMBULATORY PEDIATRICS Non specified – The Department of Pediatrics, University of Illinois College of Medicine at Rockford seeks a BC/BE pediatrician for an academic position in an ambulatory setting. The Community Health Center program is a longitudinal, comprehensive experience in primary care medicine. Each center is staffed by full-time faculty. Responsibilities include supervision of medical students in an ambulatory setting, direct patient care, quality assurance activities and clinical research. For earliest consideration please reply by: May 1, 1991. Reply with CV to: D.H. Wortmann, MD, Chairman, Department of Pediatrics, UICOM-R, 1400 Charles Street, Rockford, IL 61104. UICOM-R is an equal opportunity/affirmative action employer.

JUNIOR FACULTY POSITION in the Division of General/Ambulatory Pediatrics is available at Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas. Applicant must be board-eligible/certified. Responsibilities include teaching, patient care and clinical research. Tenure track appointment available to qualified candidates. Call or submit CV to: V.J. Gururaj, MD, Professor, Director Division General/Ambulatory Pediatrics, Texas Tech University Health Sciences Center, School of Medicine, Department of Pediatrics, Lubbock, TX 79430. (806) 743-2266.

WYOMING – University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, board-certified pediatrician to be the pediatric coordinator of an 8-8 family practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming! Contact: Dr. David Driggers, Director, University of Wyoming Family Practice Residency, 1522 East "A" Street, Casper, WY 82601. (307) 266-3076. The University of Wyoming is an affirmative action/EOE.

PLEASE NOTE – Address replies to box number ads as follows: Box number _____, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

Faculty Positions

ASSOCIATE PROFESSOR, Division of Medical Genetics, Pediatric Department, University of Utah Medical Center is seeking an individual with MD/PhD, board-eligible by American Board of Medical Genetics. Assistant Professor level with primary responsibilities including development of molecular genetics research laboratory, specifically studying neurofibromatosis and other neurocutaneous disorders. Collaboration with Department of Human Genetics, Howard Hughes Institute in the Human Molecular Biology and Genetics Program built into position. Also responsible for sharing part of clinical care in Medical Genetics Program. Send CV to: John C. Carey, MD, Chief, Division of Medical Genetics, Department of Pediatrics, UUMC, 50 North Medical Drive, Salt Lake City, UT 84132. Deadline: July 31, 1991 or until qualified applicant identified. EEO/AA employer.

BC/BE PEDIATRIC CARDIOLOGIST needed for a faculty position to join two other board-certified pediatric cardiologists in a very active service. Send CV to: Drs. Joon Park or Somkid Sridaromont, Pediatrics, Texas Tech University Health Sciences Center, Lubbock, TX 79430. (806) 743-3088. TTUHS is an equal opportunity/affirmative action employer.

THE DEPARTMENT OF PEDIATRICS of the University of Pittsburgh and Children's Hospital of Pittsburgh seeks a BC/BE pediatrician at the assistant or associate professor level to join the University Pediatric Diagnostic Referral Service. The position requires an academic generalist preferably with either chief residency experience or general academic pediatric fellowship training. Responsibilities include patient care, teaching, and clinical research, with an emphasis on inpatient care. Rank and salary commensurate with experience. Inquiries should be addressed to: J. Carlton Gartner, Jr., MD, University Pediatric Diagnostic Referral Service, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-3417. An equal opportunity employer.

PEDIATRICIAN – TENNESSEE. Vanderbilt University Medical Center Pediatrics Department seeks developmental/behavioral pediatrician for Division of Child Development at assistant or associate professor level. Responsibilities: Interdisciplinary team evaluations, clinical teaching, opportunity to pursue research. Reply to: Mark Wolraich, MD, Chief, Division of Child Development, 426 Medical Center South, 2100 Pierce Avenue, Nashville, TN 37232-3573.

Faculty Positions

PEDIATRICIAN – Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence E. Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

DEPARTMENT OF PEDIATRICS, State University New York at Buffalo/Children's Hospital seeks faculty member to join ten member Division of Neonatology. We are seeking a physician with a commitment to pursue research which can be related to perinatal circulatory physiology. We are particularly interested in the responsibility of and remodeling of the pulmonary vascular bed of the fetus and newborn. Techniques employed could range from integrated physiologic, to isolated organ or tissue, to cellular or molecular. Division conducts NIH-sponsored laboratory research on perinatal pulmonary and circulatory physiology. Clinical research includes six years of experience with surfactant therapy. MD: BE/BC neonatal-perinatal medicine. Assistant or associate professor level. CV to: Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. We are interested in identifying qualified minority and women candidates. The State University of New York at Buffalo and the Children's Hospital of Buffalo are affirmative action/equal opportunity employers. No person, in whatever relationship with the University or the Hospital, shall be subject to discrimination on the basis of age, creed, color, handicap, national origin, race, religion, sex, marital, or veteran status.

FACULTY POSITION in Neonatology – Opening for August 1, 1991 or 1992. Must be board-certified or board-eligible in neonatal/perinatal medicine. The Neonatal Program of New York University Medical Center is a balanced university program providing neonatal care to Tisch Hospital and Bellevue Hospital. Responsibilities include clinical neonatal service, teaching and the conduct of independent research. Academic rank will be commensurate with qualifications. Protected time and funds are available for research. Interested candidates should submit curriculum vitae and contact: Karen D. Hendricks-Munoz, MD, MPH, Director, Neonatal Program Department of Pediatrics, New York University Medical Center, New York, NY 10016. (212) 263-7477. An affirmative action/equal opportunity employer, encourages minority and women candidates' application.

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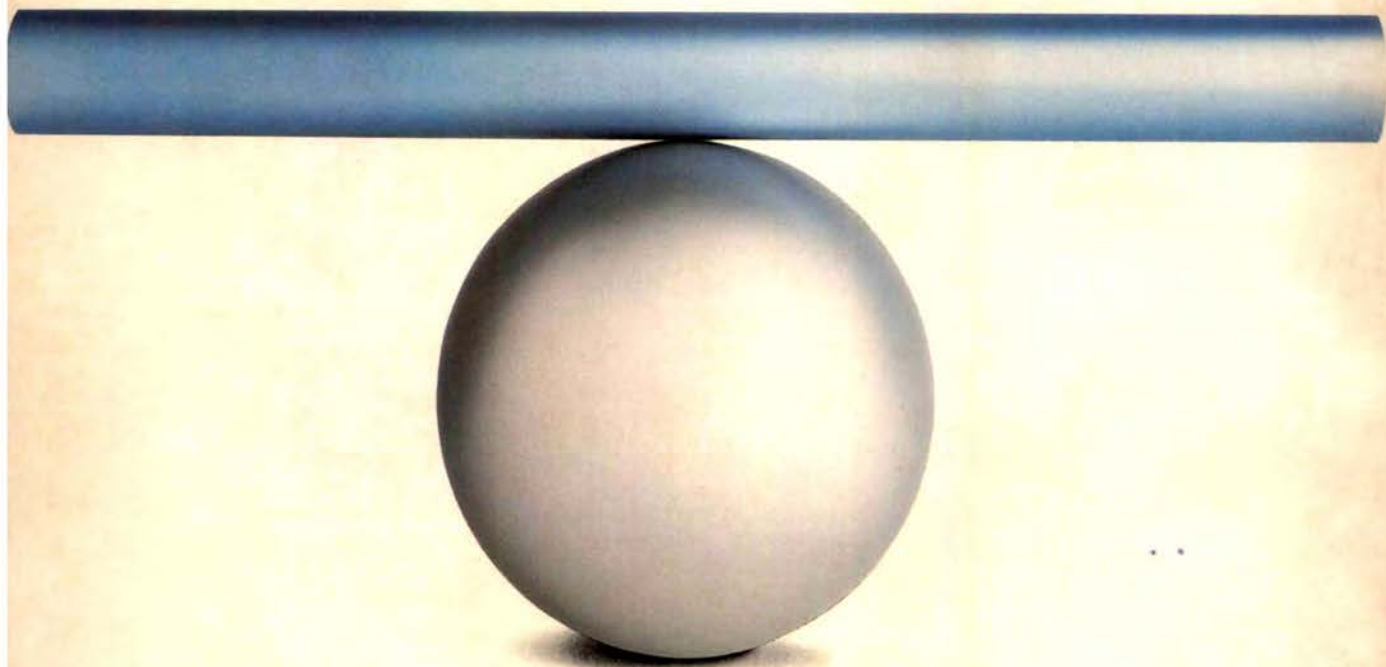
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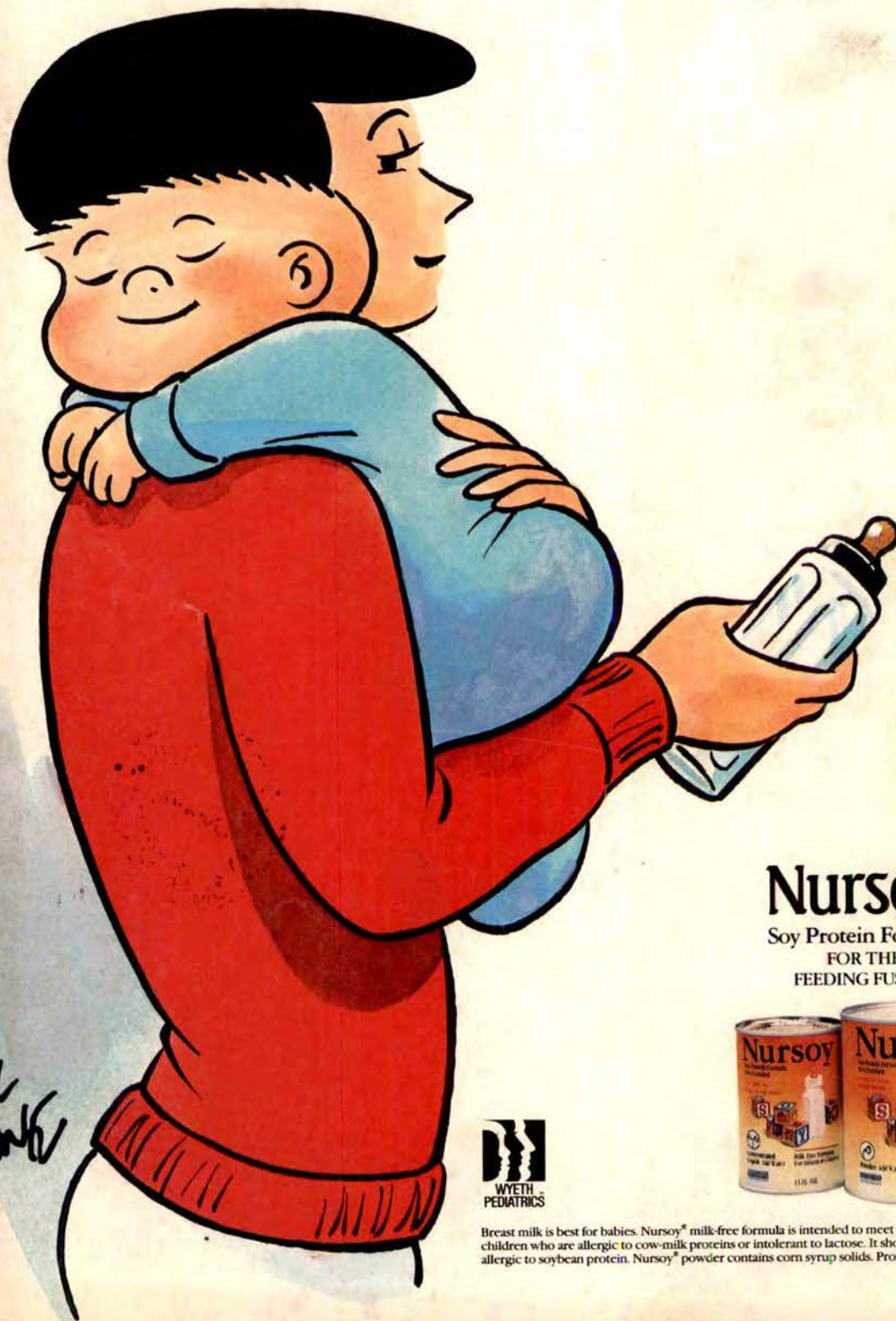
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AUGUST 1991

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Immunization Response Varies With Intensity of Acute Lymphoblastic Leukemia Therapy

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Volume 145, Number 8

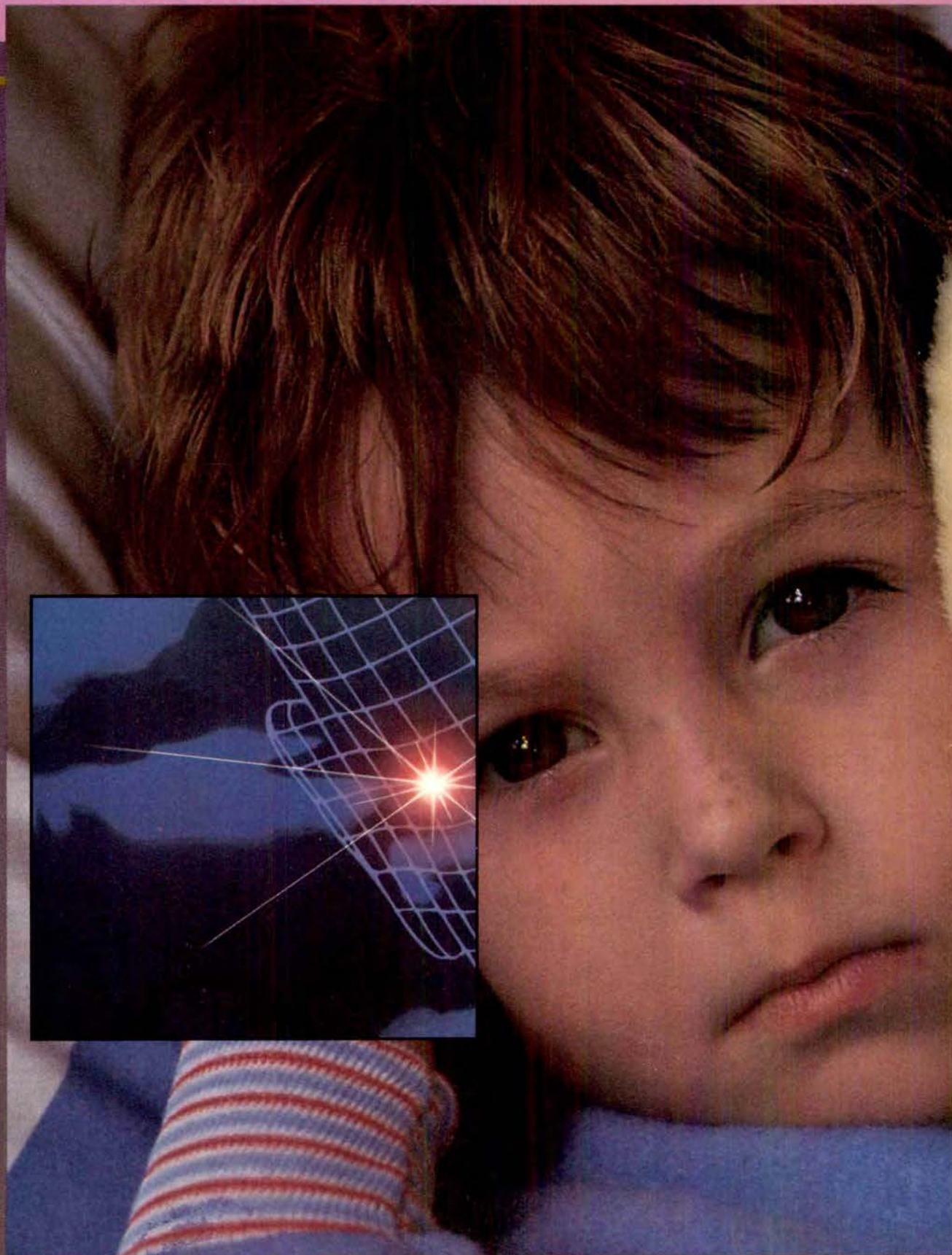
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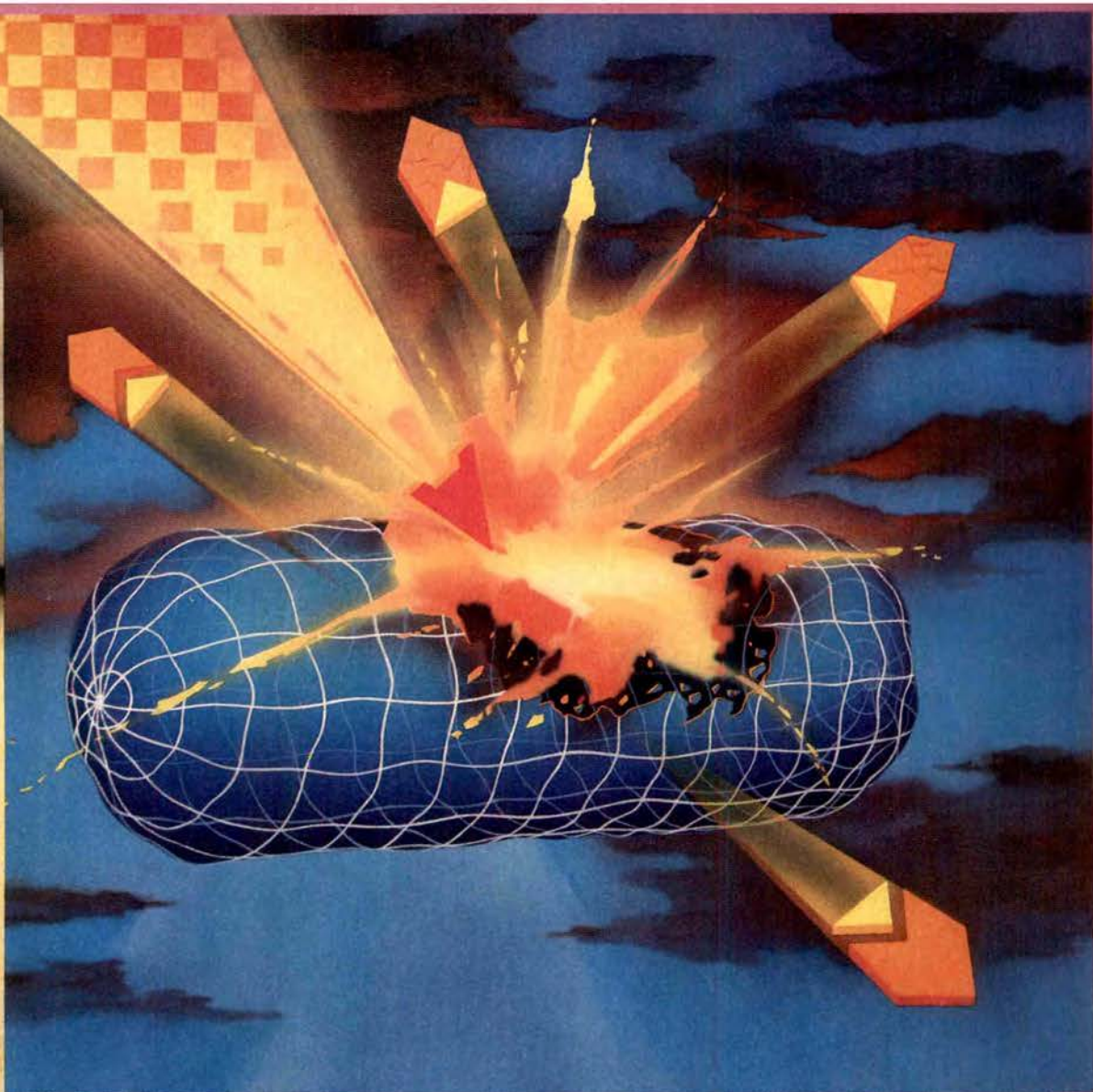
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Skin and Skin Structure Infections caused by β -lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β -lactamase-producing strains of *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β -lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication. **WARNINGS:** SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential. **Pregnancy (Category B):** Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black hairy tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthritis, myalgia and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely with the predominant effects being cholestatic, hepatocellular, or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one *Augmentin* 250 tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500 tablet every eight hours.

Since both the *Augmentin* 250 and 500 tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250 tablets are not equivalent to one *Augmentin* 500 tablet. Therefore, two *Augmentin* 250 tablets should not be substituted for one *Augmentin* 500 tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* 125 and 250 chewable tablets.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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The AMERICAN JOURNAL OF DISEASES OF CHILDREN (ISSN 0002-922X) is published monthly by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

CHANGE OF ADDRESS—POSTMASTER, send all address changes to AMERICAN JOURNAL OF DISEASES OF CHILDREN, Attention: Subscription Department, 515 N State St, Chicago, IL 60610. Notification of address change must be made at least 6 weeks in advance. Include both old and new addresses, a recent mailing label, and your new ZIP code.

Please address communications concerning accepted or published communications to AMA Specialty Journals, 515 N State St, Chicago, IL 60610.

GST registration number: R 126 225 556

AMERICAN JOURNAL OF DISEASES OF CHILDREN

AJDC

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No. 8

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WHEN IS THE VACCINE YOU USE EVERY DAY NOT THE BEST OPTION?

- **When there is an immunocompromised person in the child's household**
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Please see full Prescribing Information on following page.

DESCRIPTION: IPOL™, Poliovirus Vaccine Inactivated, produced by Pasteur Mérieux Sérums & Vaccins S.A., is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The viruses are grown in cultures of VERO cells, a continuous line of monkey kidney cells, by the microcarrier technique. The viruses are concentrated, purified, and made noninfectious by inactivation with formaldehyde. Each sterile immunizing dose (0.5 ml) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus, determined by comparison to a reference preparation. The poliovirus vaccine is dissolved in phosphate buffered saline. Also present are 0.5% of 2-phenoxyethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present. The vaccine is clear and colorless and should be administered subcutaneously.

CLINICAL PHARMACOLOGY: IPOL is a highly purified, inactivated poliovirus vaccine produced by microcarrier culture.^{1,2} This culture technique and improvements in purification, concentration and standardization of poliovirus antigen have resulted in a more potent and more consistently immunogenic vaccine than the Poliovirus Vaccine Inactivated which was available in the U.S. prior to 1988. These new methods allow for the production of vaccine that induces antibody responses in most children after administering fewer doses³ than with vaccine available prior to 1988.

Studies in developed⁴ and developing^{4,5} countries with a similar inactivated poliovirus vaccine produced by the same technology have shown that a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer.

A study in the U.S. was carried out, which involved 219 two-month-old infants who had received three doses of Poliovirus Vaccine Inactivated manufactured by the same process as IPOL except the cell substrate was primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine. Following a third dose of vaccine at 18 months of age, high titers of neutralizing antibody were present in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.⁶

Additional studies were carried out in the U.S. with IPOL. Results were reported for 120 infants who received two doses of IPOL at 2 and 4 months of age. Of these 120 children, detectable serum neutralizing antibody was induced after two doses of vaccine in 98.3% (Type 1), 100% (Type 2) and 97.5% (Type 3) of the children. In 83 children receiving three doses at 2, 4, and 12 months of age detectable serum neutralizing antibodies were detected in 97.6% (Type 1) and 100% (Types 2 and 3) of the children.^{7,8}

Poliovirus Vaccine Inactivated reduces pharyngeal excretion of poliovirus.⁹⁻¹² Field studies in Europe have demonstrated immunity in populations thoroughly immunized with another IPV.¹³⁻¹⁷ A survey of Swedish children and young adults given a Swedish IPV demonstrated persistence of circulating antibodies for at least 10 years to all three types of poliovirus.¹³

Paralytic polio has not been reported in association with administration of Poliovirus Vaccine Inactivated.

INDICATIONS AND USAGE: Poliovirus Vaccine Inactivated is indicated for active immunization of infants, children and adults for the prevention of poliomyelitis. Recommendations on the use of live and inactivated poliovirus vaccines are described in the ACIP Recommendations^{18,19} and the 1988 American Academy of Pediatrics Red Book.²⁰

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations: It is recommended that all infants, unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.¹⁸ Poliovirus Vaccine Inactivated should be offered to individuals who have refused Poliovirus Vaccine Live Oral Trivalent (OPV) or in whom OPV is contraindicated. Parents should be adequately informed of the risks and benefits of both inactivated and oral polio vaccines so that they can make an informed choice (Report of an Evaluation of Poliomyelitis Vaccine Policy Options, Institute of Medicine, National Academy of Sciences, Washington, D.C., 1988).

OPV should not be used in households with immunodeficient individuals because OPV is excreted in the stool by healthy vaccinees and can infect an immunocompromised household member, which may result in paralytic disease. In a household with an immunocompromised member, only Poliovirus Vaccine Inactivated should be used for all those requiring poliovirus immunization.²⁰

Children Incompletely Immunized: Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see DOSAGE AND ADMINISTRATION).

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with Poliovirus Vaccine Inactivated.

ADULTS

General Recommendations: Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the U.S. is not recommended. Adults who have increased risk of exposure to either vaccine or wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the DOSAGE AND ADMINISTRATION section.¹⁸

- The following categories of adults run an increased risk of exposure to wild polioviruses:¹⁹
- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.
- Incompletely vaccinated or unvaccinated adults in a household (or other close contacts) with children given OPV provided that the immunization of the child can be assured and not unduly delayed. The adult should be informed of the small OPV related risk to the contact.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

Patients with recognized immunodeficiency are at greater risk of developing paralysis when exposed to live poliovirus than persons with a normal immune system. Under no circumstances should oral live poliovirus vaccine be used in such patients or introduced into a household where such a patient resides.¹⁸

Poliovirus Vaccine Inactivated should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antimetabolites or radiation. Patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of Poliovirus Vaccine Inactivated.²¹

CONTRAINDICATIONS: Poliovirus Vaccine Inactivated is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including neomycin, streptomycin and polymyxin B.

If anaphylaxis or anaphylactic shock occurs within 24 hours of administration of a dose of vaccine, no further doses should be given.

Vaccination of persons with any acute, febrile illness should be deferred until after recovery; however, minor illnesses such as mild upper respiratory infections are not in themselves reasons for postponing vaccine administration.

WARNINGS: Neomycin, streptomycin, and polymyxin B are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see DESCRIPTION) and allergic reactions may occur in persons sensitive to these substances.

PRECAUTIONS: General: Before injection of the vaccine, the physician should carefully review the recommendations for product use and the patient's medical history including possible hypersensitivities and side effects that may have occurred following previous doses of the vaccine.

Epinephrine hydrochloride (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Concerns have been raised that stimulation of the immune system of a patient with HIV infection by immunization with inactivated vaccines might cause deterioration in immunologic function. However, such effects have not been noted thus far among children with AIDS or among immunosuppressed individuals after immunizations with inactivated vaccines. The potential benefits of immunization of these children outweigh the undocumented risk of such adverse events.¹⁸

Drug Interactions: There are no known interactions of Poliovirus Vaccine Inactivated with drugs or foods. Simultaneous administration of other parenteral vaccines is not contraindicated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY: REPRODUCTIVE STUDIES — PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with Poliovirus Vaccine Inactivated. It is also not known whether Poliovirus Vaccine Inactivated can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Poliovirus Vaccine Inactivated should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE: Safety and efficacy of IPOL have been shown in children 6 weeks of age and older^{6,8} (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed during a clinical trial.⁶ Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures $\geq 39^{\circ}\text{C}$ ($\geq 102^{\circ}\text{F}$) were reported in up to 38% of vaccinees. Other symptoms noted included sleepiness, fussiness, crying, decreased appetite, and spitting up of feedings. Because Poliovirus Vaccine Inactivated was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given without IPV.

In another study using IPOL in the United States, there were no significant local or systemic reactions following injection of the vaccine. There were 7% (6/86), 12% (8/65) and 4% (2/45) of children with temperatures over 100.6°F, following the first, second and third doses respectively. Most of the children received DTP at the same time as IPV and therefore it was not possible to attribute reactions to a particular vaccine; however, such reactions were not significantly different than when DTP is given alone.

Although no causal relationship between Poliovirus Vaccine Inactivated and Guillain-Barré Syndrome (GBS) has been established,²² GBS has been temporally related to administration of another Poliovirus Vaccine Inactivated.

NOTE: The National Childhood Vaccine Injury Act of 1986 requires the keeping of certain records and the reporting of certain events occurring after the administration of vaccine, including the occurrence of any contraindicating reaction. Poliovirus Vaccines are listed vaccines covered by this Act and health care providers should ensure that they comply with the terms thereof.²³

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration. If these conditions exist, vaccine should not be administered.

After preparation of the injection site, immediately administer the vaccine subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In adults the vaccine should be administered in the deltoid area.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

CHILDREN

Primary Immunization: A primary series of IPOL consists of three 0.5 ml doses administered subcutaneously. The interval between the first two doses should be at least four weeks, but preferably eight weeks. The first two doses are usually administered with DTP immunization and are given at two and four months of age. The third dose should follow at least six months but preferably 12 months after the second dose. It may be desirable to administer this dose with MMR and other vaccines, but at a different site, in children 15-18 months of age. All children who received a primary series of Poliovirus Vaccine Inactivated, or a combination of IPV and OPV, should be given a booster dose of OPV or IPV before entering school, unless the final (third dose) of the primary series was administered on or after the fourth birthday.¹⁸

The need to routinely administer additional doses is unknown at this time.¹⁸

A final total of four doses is necessary to complete a series of primary and booster doses. Children and adolescents with a previously incomplete series of IPV should receive sufficient additional doses to reach this number.

ADULTS

Unvaccinated Adults: For unvaccinated adults at increased risk of exposure to poliovirus, a primary series of Poliovirus Vaccine Inactivated is recommended. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, 3 doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. If less than 1 month is available, a single dose of either OPV or IPV is recommended.

Incompletely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than 3 doses of conventional IPV or a combination of conventional IPV or OPV totalling fewer than 3 doses should receive at least 1 dose of OPV or Poliovirus Vaccine Inactivated. Additional doses needed to complete a primary series should be given if time permits.

Completely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of either OPV or IPV.¹⁸

HOW SUPPLIED: Syringe, 0.5 ml with integrated needle (1 x 1 Dose package and 10 x 1 Dose package) — Product Nos. 49281-8605-1 and 49281-8605-2.

STORAGE: The vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F and 46°F). The vaccine must not be frozen.

- REFERENCES:** 1. van Wezel, A.L., et al. Inactivated poliovirus vaccine: Current production methods and new developments. *Rev Infect Dis* 6 (Suppl 2): S335-S340, 1984. 2. Montagnon, B.J., et al. Industrial scale production of inactivated poliovirus vaccine prepared by culture of Vero cells on microcarrier. *Rev Infect Dis* 6 (Suppl 2): S341-S344, 1984. 3. Salk, J., et al. Antigen content of inactivated poliovirus vaccine for use in a one- or two-dose regimen. *Ann Clin Res* 14: 204-212, 1982. 4. Salk, J., et al. Killed poliovirus antigen titration in humans. *Develop Biol Standard* 41: 110-132, 1978. 5. Salk, J., et al. Theoretical and practical considerations in the application of killed poliovirus vaccine for the control of paralytic poliomyelitis. *Develop Biol Standard* 47: 181-198, 1981. 6. McBean, A.M., et al. Serologic response to oral polio vaccine and enhanced-potency inactivated polio vaccines. *Am J Epidemiol* 128: 615-628, 1988. 7. Unpublished data available from Pasteur Mérieux Sérums & Vaccins S.A. 8. Faden, H., et al. Comparative evaluation of immunization with live attenuated and enhanced potency inactivated trivalent poliovirus vaccines in childhood: Systemic and local immune responses. *J Infect Dis* 162: 1291-1297, 1990. 9. Marine, W.M., et al. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children. A family study during a Type 1 poliomyelitis epidemic. *Amer J Hyg* 76: 173-175, 1962. 10. Bottiger, M., et al. Vaccination with attenuated Type 1 poliovirus, the Chat strain. II. Transmission of virus in relation to age. *Acta Paed Scand* 55: 416-421, 1966. 11. Dick, G.W.A., et al. Vaccination against poliomyelitis with live virus vaccines. Effect of previous Salk vaccination on virus excretion. *Brit Med J* 2: 266-269, 1961. 12. Wehrle, P.F., et al. Transmission of poliovirus. III. Prevalence of polioviruses in pharyngeal secretions of infected household contacts of patients with clinical disease. *Pediatrics* 27: 762-764, 1961. 13. Bottiger, M. Long-term immunity following vaccination with killed poliovirus vaccine in Sweden, a country with no circulating poliovirus. *Rev Infect Dis* 6 (Suppl 2): S545-S551, 1984. 14. Chin, T.D.Y. Immunity induced by inactivated poliovirus vaccine and excretion of virus. *Rev Infect Dis* 6 (Suppl 2): S369-S370, 1984. 15. Salk, D. Herd effect and virus eradication with use of killed poliovirus vaccine. *Develop Biol Standard* 47: 247-255, 1981. 16. Bjerk, H. Surveillance and control of poliomyelitis in the Netherlands. *Rev Infect Dis* 6 (Suppl 2): S451-S456, 1984. 17. Lapinleimu, K. Elimination of poliomyelitis in Finland. *Rev Infect Dis* 6 (Suppl 2): S457-S460, 1984. 18. Immunization Practices Advisory Committee (ACIP). Poliomyelitis Prevention: Enhanced-Potency Inactivated Poliovirus Vaccine Supplementary Statement. *MMWR* 36: 795-798, 1987. 19. ACIP. Poliomyelitis Prevention. *MMWR* 31: 22-26 and 31-34, 1982. 20. Report of the Committee on Infectious Diseases, American Academy of Pediatrics. 21st ed: 334-342, 1988. 21. ACIP. Immunization of children infected with human T-lymphotropic virus type III/lymphadenopathy-associated virus. *MMWR* 35: 595-606, 1986. 22. WHO. Weekly Epidemiology Record 54: 82-83, 1979. 23. National Childhood Vaccine Injury Act. Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 37: 197-200, 1988.

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Product Information
as of December 1990
Printed in U.S.A.

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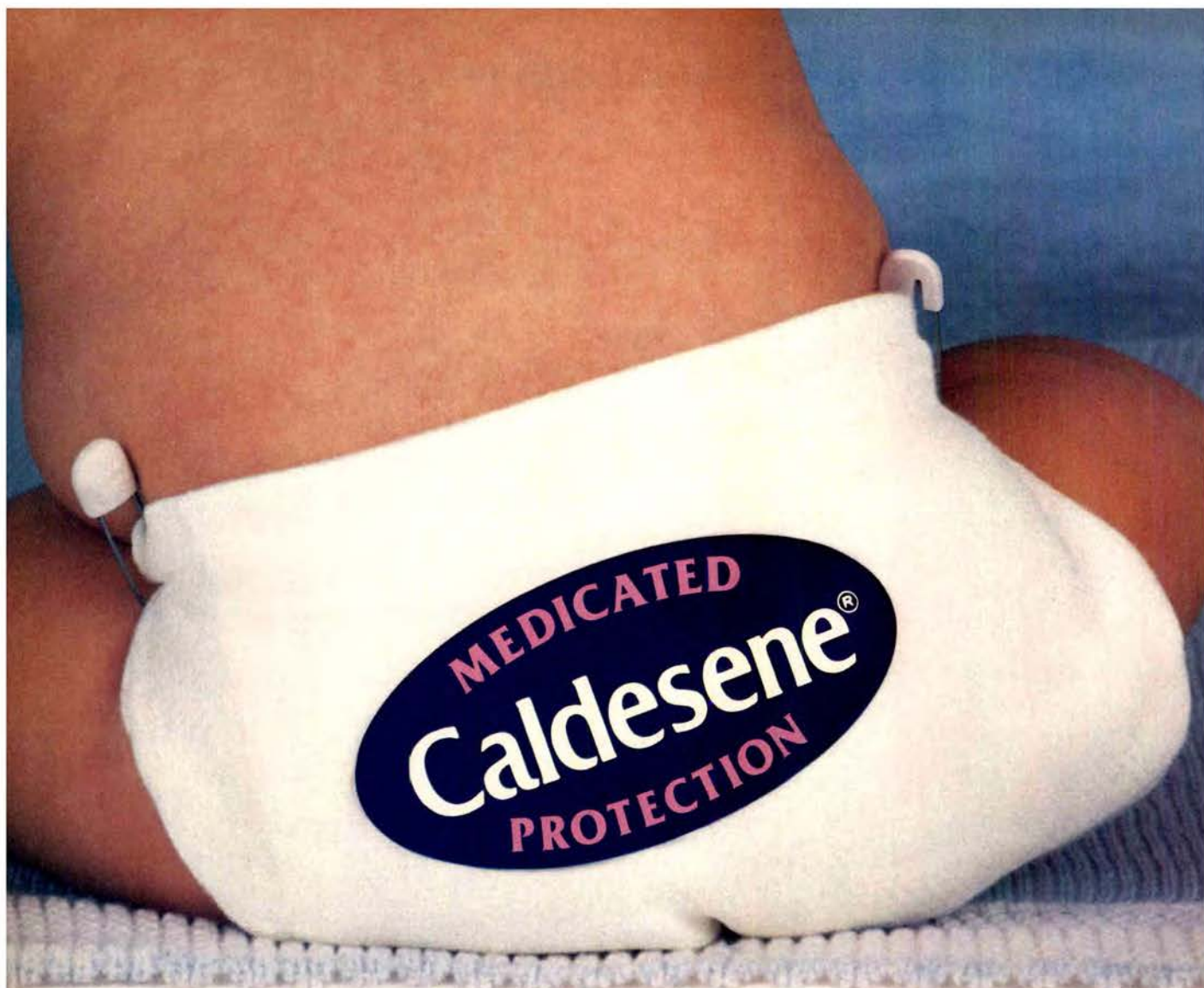
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Superior reduction for fevers over 102.5°F

PediaProfen™

Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in PediaProfen labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on PediaProfen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSEAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)—

orange, berry-vanilla flavored

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Child Welfare: The Phantom of the Health Care System

Sir.—The problem of infants requiring prolonged hospitalization for lack of appropriate discharge placements has resulted in a new population of children receiving medical care. These children have been called "boarder babies," and their numbers are steadily increasing. On a given day in Philadelphia, Pa, 70 boarder babies are in hospitals awaiting discharge. They limit access to medical care for other children by occupying beds and increasing the hospitals' operating costs.

This is one of the most insidious side effects of the current crack cocaine epidemic, resulting in the abandonment of numerous infants in hospitals. It has resulted in what one author describes as "the youngest of the homeless."¹

A June 1989 survey¹ by the Child Welfare League of America of hospitals in five American cities identified 304 boarder babies in the 54 hospitals reporting cases. At least 69% of the identified babies showed signs of impairment due to the mother's drug habits.

The reason for the continuation of hospitalization following completion of medical goals generally falls into two categories. The first is the abandonment by families unwilling to provide care. This group contains many of the cocaine-addicted mothers. In Philadelphia alone, it is estimated that 16.4% of the more than 28 000 babies born annually will have been exposed to cocaine in utero. In just 1 year, that city will have another 4500 potentially drug-damaged children for whom to plan. Approximately 10% of these children will require some form of substitute care after birth.

The second group includes the technology-dependent, medically

fragile child whose family is unable to provide appropriate care at home. This group includes many single-parent, low-income families for whom medical assistance does not reimburse for sufficient support services in the home. A committed secondary care provider is unavailable in many cases, and the child welfare system is faced with the challenge of finding a medically sophisticated foster home for these children.

The number of special-needs children in Philadelphia increased from 79 in fiscal year 1986 to 467 in fiscal year 1990. The cost of providing services to these children grew from \$2.9 million to approximately \$16.1 million in that time.² The response by the state and federal legislatures for increased support for these children has been sluggish, and consequently many of these infants remain in tertiary care or intermediate care hospitals due to lack of funds.

This problem adversely affects both the health of individual children and the health of medical practice by causing inappropriate utilization of hospital beds. The pediatric community has an obligation to understand the child welfare system and advocate for its mission. Through programs such as the American Academy of Pediatrics' "Healthy Partnership for Children," pediatricians can participate in innovative programs that directly impact community issues. Pediatricians can become involved with their local child welfare system by serving on advisory boards and providing medical input to a system that is struggling with comprehending medical issues.

For too long, the child welfare system has been regarded as the "phantom of the health care system," an unseen and sinister actor in the tragedy that affects many of our sickest and most vulnerable children. It is time for pediatricians, social workers, educators, and bureaucrats to form al-

liances that will result not only in preventive programs to improve health, but also in "care providing" programs that offer services to children and families who desperately require aid.

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1. Munns JM. The youngest of the homeless: characteristics of hospital boarder babies in five cities. Presented at the Child Welfare League of America; August 2, 1989.

2. Philadelphia, Pa, City Council Operating Budget Hearings, April 23, 1990 (testimony of Joan M. Reeves, commissioner of the Department of Human Services, Philadelphia).

Resident and Nurse Practitioners: Responding to Education and Patient Care Needs

Sir.—In recent issues of *AJDC*, Bedrick^{1,2} and Winter³ address the issue of residency work demands and the overburden in terms of hours and responsibility that hinder the effectiveness and humanity of the physician education process. They suggest that to hire more house staff to limit the number of resident working hours is not the answer to the problem. Likewise, expanding the number of residents in a given program to meet the ever-increasing service demands of the current tertiary and quaternary care centers will not meet service needs or optimize a resident's educational experience. Other practical ways are needed to address the problems associated with resident overwork and hospital care needs.

The use of nonphysician primary care providers in the inpatient hospital setting bears further comment. Before a solution is implemented,

physicians should analyze the available data to ensure that quality of patient care is maintained. It is also imperative to ensure that the implementation of a new care modality maintains or increases a resident's learning time and educational experience. We would like to explore the reality of using nurse practitioners and physician assistants as primary health care providers in the inpatient setting.

A number of published reports have discussed the use of nonphysicians in providing primary care. Studies show that skilled primary care providers, such as nurse practitioners, can perform specific patient care responsibilities usually assigned to house staff. Responsibilities include such functions as admitting patients, assessing the initial and subsequent status of patients, obtaining histories and performing physical examinations, and performing laboratory evaluations and therapeutic procedures. As we transfer these duties to nonphysicians and then evaluate the outcome, it may mean that fewer residents are needed to meet the increasing service demands, and the resident educational experience might be enhanced.

A necessary phase in using nonphysician health care providers is to test their effectiveness in the clinical area. We need to write job descriptions for the nurse who functions in the role of health associate or associate resident. We must document the effectiveness of this new role and its effect on patient care and resident education. Will resident time, in fact, be redirected to educational pursuits? Will quality of patient care be maintained? Will the nurse practitioners be integrated into the patient care role or will they be relegated to work not desired by the residents? The bulk of the material published to date has dealt with the issue of quality of care, and very little data exist to provide an answer to our other questions.^{4,5} This is a concern in view of the impact and magnitude of the changes proposed.

The University of Colorado, Denver has been a leader in the pediatric nurse practitioner movement and in the integration of nonphysician health care providers. Silver and McAtee^{6,7} have published reports in

medical and nursing journals discussing the evolving role of the pediatric nurse practitioner in both the inpatient and outpatient environment. In addition, Silver et al⁸ championed the development of a specially trained physician assistant, the child health associate, to provide primary care in the ambulatory setting. The reports by Silver and McAtee center on efforts to confirm the notion that nonphysicians can provide care to pediatric patients comparable with that provided by a first-year resident.

Research supports this practice in a setting in which a trained professional works with an experienced senior colleague. Nurse practitioners are effective, competent, and capable of providing high-quality care in the hospital setting as well.⁹ The nurse practitioner in the University of Colorado's program for hospital-based pediatric nurse practitioners was capable of the following: (1) admitting patients; (2) assessing both initial clinical states and subsequent changes in a patient's condition; (3) writing relevant orders; (4) performing a variety of complex diagnostic and therapeutic procedures, including lumbar punctures and thoracenteses; (5) ordering and integrating laboratory studies; (6) counseling patients and family members; (7) discharging patients; and (8) performing other traditional nurse practitioner duties.

They were further trained to share primary responsibility for inpatient care and to make independent value judgments regarding the health status of the patient. Silver and McAtee^{6,7} stated that the expanded hospital nurse practitioner's role can be practiced most effectively in urban nonteaching hospitals or in rural hospitals where no direct competition would occur with residents, interns, or medical students. They suggest the use of nurse associate residents. These individuals are nurse practitioners, clinical nurse specialists, or other nurse specialists who receive several months of formal preparation that equips them to substitute for house officers in teaching hospitals. Nurse associate residents would participate in all house staff activities, including regularly assigned rotations and night call. They maintain their

identity as nurses and function as members of the health care team. The proposed nurse associate residents could substitute for up to 5% to 10% of the house staff in the oversupplied subspecialties.

Few data are available to suggest that using nonphysicians improves the educational experience for the resident. Major issues, such as daytime and nighttime supervision of the nonphysician, remain unanswered. Would the senior resident serve as a supervisor for these traditionally attending supervised professionals?

Sox,⁴ in his review of 10 years of literature on nonphysician primary health care providers in outpatient care, found 21 articles that offered comparisons of care between the nonphysician practitioner and physicians. His finding was that nurse practitioners and physician assistants provide care that is indistinguishable from the care provided by physicians in the outpatient setting. Because of the variable research methods, there was no experimental basis on which this finding could be generalized to settings outside the office, to unsupervised care, or to care of the seriously ill patient. Once again, no data were provided to determine the impact of using such health care providers on the educational experience of the resident.

The problem of resident education needs and hospital service demands remains. This discussion demonstrates that the use of nonphysicians has potential, but not all pertinent questions have been addressed. Staffing needs may be met but resident educational needs may or may not be served. The easy solution is to use the residents for whatever is dictated by the hospital. The more difficult solution will involve a reconfiguration of the health care setting and an insistence on excellent patient care in the context of rational educational planning for residents. Rather than embracing more and more in the service area with a consequent increase in the number of residents, we need to attend to the educational needs of the residents. Decisions on hospital staffing should be based on patient care and resident education needs, not merely on economic constraints

or the availability of other health care professionals.

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1. Bedrick AD. The eighty-hour work-week: residency friend or foe? *AJDC*. 1990;144:857.
2. Bedrick AD. In reply to: Winter RJ. Neonatology and residency training. *AJDC*. 1990;144:953-954.
3. Winter RJ. Neonatology and residency training. *AJDC*. 1990;144:953.
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Priorities in Academic Pediatrics

Sir.—I found it interesting to read Goetzman's comments¹ in the December 1990 issue of *AJDC* concerning the effects of selecting a new department head. As a practicing physician, I had no insight into some of what he mentioned. I was struck, however, by the comment that junior faculty members are said to "sacrifice" their careers if they are to "keep clinical programs afloat." In other words, caring for the sick will interfere with the need to publish. In the editorial by Bier et al² in the same issue, several editors discuss their methods for dealing with "self-

plagiarism." The motivation for this activity is to enlarge the physician's list of publications.

In reality, the cause of "self-plagiarism" is the mind-set evidenced by Goetzman's comments. I have no quarrel with research. All of what I do is based on what researchers have done before me. However, I have a somewhat different perception of the reality of health care in the United States. We live in a place and time in which many children do not have access to basic health care services and immunizations. In spite of reports of various committees, it is clear that there is a profound shortage of practicing general pediatricians. The problem with pediatric practice is not money; the pay is fine and I doubt that researchers make any more. The problem is the attitude of the medical center. In my group of 25 residents at a major children's hospital, only one went into practice. The others followed their favored role models and went into academic medicine. Thus, *AJDC* can publish articles on liver transplantation, extracorporeal membrane oxygenation, and prolonged intubation in a society that cannot even properly control measles.

I harbor no ill will toward Goetzman, but I do have a suggestion for him and other department chairmen who read *AJDC*. They should start hiring and promoting physicians who want to perform clinical work. Every medical center has them, the lifelong assistant professors who are in the hospital day and night treating patients but never seem to get anything published. The residents would then see the value of clinical pediatrics and would be more likely to enter that arena. In addition, a medical center that emphasizes clinical work over research is going to get far more referrals from the "local medical doctors." Research is important, but so is caring for children who do not have rare, interesting conditions.

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1. Goetzman B. The editorial board speaks: appointment vs anointment. *AJDC*. 1990;144:1291.

2. Bier DM, Fulginiti VA, Garfunkel JM, et al. Duplicate publication and related problems. *AJDC*. 1990;144:1293-1294.

In Reply.—The development of special academic series for faculty members heavily involved in patient care is becoming widespread in academic medical centers in this country. Faculty in such series must make creative contributions in the clinical arena, but the pressure on them is significantly reduced in recognition of their major time commitment to patient care. It is hoped that this will help alleviate the problem that Jacobs addresses. In this age of medical specialization and subspecialization, it has taken quite a while to recognize that faculty members also become more expert at one of the traditional academic modes of university service, ie, teaching, research, and public service, when clinical activities are a central part of these duties. Thus, it is becoming more and more rare in academic medicine for an individual to be excellent in all three roles. As the pendulum swings, let us hope that it swings far enough to put the emphasis on teaching that it deserves.

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Thumb-Sucking

Sir.—Because my oldest son was a thumb-sucker who also carried a blanket and now needs orthodontic correction of malaligned teeth, I was particularly interested in the recent article by Friman.¹

Thumb-sucking seems to be fairly common, yet Friman studied only eight patients. This seems like a very small sample size considering the prevalence of this problem. The eight patients who were followed up seem to have been preselected in a sense, not only because of the general inclusion criteria, but also because of the apparent motivation to stop thumb-sucking exhibited by both the children and their parents. Thumb-sucking, with or without other object

attachment, is a very common problem. Therefore, it seems to me that Friman could have studied a much larger patient group and reached much more valid conclusions. Similar problems occur in studies in orthopedic surgery, especially those in which the natural history of a disease or a specific treatment modality is followed up. Although a number of reports purport to be long-term follow-up studies of various conditions, data from 25% to 50% of the initial group of study patients are often unavailable at the study's conclusion. One always wonders what happened to those others who are no longer represented and what effect their inclusion would have had on the final results. The size of a study group should be proportional to the prevalence of the problem and/or the importance of the problem if the conclusions are to be valid.

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1. Friman PC. Concurrent habits: what would Linus do with his blanket if his thumb-sucking were treated? *AJDC*. 1990;144:1316-1318.

In Reply.—I appreciate Dr Lubicky's interest in my study of concurrent habits, but he has misunderstood it in two ways. First, it was not a study of thumb-sucking per se, but rather of covariation between chronic thumb-sucking and object attachment (ie, the "Linus" syndrome). To study this covariation, I treated thumb-sucking and measured, but did not treat, attachment. I followed guidelines derived from a thorough literature review for treatment of thumb-sucking.^{1,2} These guidelines recommend that only children aged 5 years or older be treated to reduce thumb-sucking, and then only if the habit is chronic (ie, occurs in more than one environment, such as at home and at school). Thumb-sucking is common in young children, but chronic thumb-sucking in children aged 5 years and older is not. No incidence figures are available, but my estimate, based on 9 years of research on thumb-sucking, is that about 5% to 10% of thumb-sucking children older than age 5 years have a chronic habit.

I also estimate that only about one third of these children are strongly attached to an object. Thus, as a representative sample of simple thumb-sucking, eight children is quite small, as Dr Lubicky points out. But as a representative sample of children with the true "Linus" syndrome, eight is substantial. Still, additional study with larger samples is desirable.

Second, my study focused on a behavioral process, not on an actuarial outcome.³ If I had wanted an actuarial outcome (eg, the number of children in a given population who would respond to treatment), I would have recruited a much larger sample and used a group design. Instead, I recruited a smaller sample for intensive study of the behavioral process resulting from treating thumb-sucking and ignoring concurrent object attachment. Research on covariation between childhood habits is new, and, at this stage, process questions are much more informative and important than actuarial questions. Single subject (N=1) research designs such as the multiple baseline used in my article are ideally suited to such study because they reveal the relationship between dependent and independent variables over time. These designs also have a very high degree of internal validity, the reasons for which include multiple direct observations and multiple direct replications in the study. Furthermore, in the domain of N=1 research, eight baselines (eight direct replications) is quite high.⁴ Thus, contrary to Dr Lubicky's suggestion about small sample size, my sample of eight is large given the research question and design of my study. I do share Dr Lubicky's belief in the value of an actuarial outcome from treatment-based research on concurrent habits, but pursuing such an outcome without first more fully understanding the relationship between the habits would be premature. I request that he have what I must have in pursuit of my research on concurrent habits: patience.

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1. Friman PC, Schmitt BD. Thumb sucking in childhood: pediatrician's guidelines. *Clin Pediatr*. 1989;28:438-440.

2. Friman PC, Leibowitz JM. An acceptable and effective treatment alternative for chronic thumb and finger sucking. *J Pediatr Psychol*. 1990;15:57-65.

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4. Kratochwill TR. *Single Subject Research: Strategies for Evaluating Change*. Orlando, Fla: Academic Press Inc; 1978.

The 80-Hour Workweek and Residency Programs: Closing Arguments

Sir.—*AJDC* recently published two commentaries by me concerning the educational goals (vs service needs) of resident rotations in the neonatal intensive care unit¹ and the implications of an 80-hour workweek for pediatric residents.² In these pieces, I reflected on the potential impact of these issues on the educational curricula of pediatric postgraduate programs. Now, after several months of "lively discussion," not only in *AJDC*, but with residents and faculty at my own institution, it is appropriate now for me to present some additional thoughts and "closing arguments."

Concerns that excess workloads result in overstressed physicians and ensuring that residents go home to sleep after a rigorous night on call are important as we design optimal residency educational curricula. However, dwelling on these topics at the expense of the learning process may sidestep some of the more pressing issues about postgraduate residency training.

The long working hours of practicing pediatricians (and residents) are legion. Why do these clinicians persist in their daily duties and responsibilities despite working long hours with sick patients? It is certainly not the lure of vast wealth and bankers' hours! Few of us went into pediatrics expecting to work a 40-hour week. We did so because of the profound satisfaction in and enjoyment of our

chosen specialty and that special feeling that occurs when a critically ill patient or family takes that extra moment to express their gratitude.

Residency training and its inherent educational goals should not be an endurance test. Even though house officers may work long hours and stay up all night, they experience and savor the same nonremunerative rewards as do attending physicians. Residents should enjoy their work (and I believe that most do!). I believe that many residents experience some of their most valued educational moments while on call. Conversely, some house officers recall that the worst moments of their residencies occurred while on call. The reality of the situation is that being on call is not always a great experience, but we need to make the best of it. It is important to temper idealism with reality.

Residents in postgraduate education must have an appreciation and understanding of the natural history of pediatric medical disorders. A "postcall" (the period or state of mind immediately following an overnight shift of in-hospital call, usually commencing at 8 AM) resident will not do himself or herself any favors by admitting a patient in diabetic ketoacidosis at 7 AM, writing admitting orders for a continuous insulin infusion, and signing out the patient at 8 AM without participating in that patient's ongoing care, let alone learning about the pathophysiology and treatment of diabetes mellitus. The timing of educational opportunities cannot be managed by punching a time clock; neither can resident work hours.

We can all recall numerous instances when residents were up all night with sick patients, but insisted on being involved in their patients' care most of the following day because of a genuine concern for their patients and an interest in their own education. These residents were indeed tired the next day, but they felt that a more significant process was occurring and that an important goal was being met. They were excited about what they were doing and learned despite a nagging fatigue. These individuals were now one rung higher on their educational ladder. Yes, they went home tired, but they had the personal satisfaction of know-

ing that they had done a good job. I know that not all (perhaps few) residents have felt this way; some nights on call (or postcall days) may not permit ideal educational experiences.

Residents need time to attend to personal and family needs; their call schedules need to accommodate these priorities. The "good old days" were far from perfect. Our present system is considerably better. However, we should continue making improvements in the residency educational process to prepare house officers not only for satisfying careers in pediatrics, but for a fulfilling life outside the office. The era of 36-hour shifts must end. Weary residents can make mistakes, but as educational programs improve, we can minimize such mistakes. Above all, we must not teach our residents that pediatrics can be learned and eventually practiced while punching a time clock. As educators, we will do our students and patients an injustice by conveying this type of mind-set.

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2. Bedrick AD. The eighty-hour workweek: residency friend or foe? *AJDC*. 1990;144:857.

Child Sexual Abuse and Human Immunodeficiency Virus Transmission

Sir.—The article by Gutman et al¹ on human immunodeficiency virus (HIV) transmission by child sexual abuse in the February 1991 issue of *AJDC* can be misleading. The authors found that the incidence of sexual abuse among the 96 children who tested positive for HIV was 14.6%. The accepted incidence of sexual abuse in the general population is one in six, or 17%.² If one were to examine any group of children for signs of sex-

ual abuse, leukemia, or the common cold, one would expect to come up with a similar figure. It appears that HIV-positive children are at no increased risk of abuse.

I agree with the authors that it is important to identify those children who are HIV positive and have been sexually abused, because some immediate and delayed behavioral sequelae of child sexual abuse may put the child and adult survivor at increased risk of exposure to HIV infection or transmission of HIV to others.

I have found that positive HIV test results in children abused by perpetrators at high risk for acquired immunodeficiency syndrome has been low. To date, I have found none. I have followed up four children who were abused by HIV-positive perpetrators and they have proven to be negative for HIV 2 years after the abuse. Other centers have had similar experience.

The estimated incidence of HIV positivity in the general population is about 1 in 250.³ We have seen over 6000 sexually abused children. To date, I have not found one with evidence of HIV infection, which suggests that these children are not at increased risk of HIV infection.

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1. Gutman LT, St Claire KK, Weedy C, et al. Human immunodeficiency virus transmission by child sexual abuse. *AJDC*. 1991;145:137-141.

2. Greenwood CL, Tangalos EG, Maruta T. Prevalence of sexual abuse, physical abuse, and concurrent traumatic life events in a general medical population. *Mayo Clinic Proc*. 1990;65:1067-1071.

3. Centers for Disease Control. HIV prevalence estimates and AIDS case projections for the United States. *MMWR*. 1990;39:1-31.

In Reply.—Dr Monteleone has made several points worthy of reply. First, he notes that the incidence rate of sexual abuse in the general population is 17%. Studies that lead to prevalence rates of that level define sexual abuse broadly (a definition we endorse). However, many of the abusive activities are only minimally physically invasive, such as viewing, fondling,

kissing, rubbing, photographing, and so forth. These activities would not cause the traumatic injuries that resulted in the genital physical findings that were described in 13 of the 14 children in the present study. This is in contrast to the situation for the majority of sexually abused children in whom significant physical findings resulting from the abuse are not found. Therefore, compared with other groups of abused children, and as was noted in the original article, the abuse of the children in our study was unusually severe. We were not prospectively evaluating every child for all forms of sexual abuse; were we to have done so, our percentage would undoubtedly have risen to well above 14.6%.

The fact that Dr Monteleone has not yet identified an infected child in his clinic may reflect several factors. First is the maturity of the HIV epidemic in the communities from which his patients come. The median HIV seroprevalence in four St Louis women's clinics was 0.2% through 1989.¹ In a conversation with Rebecca Meriwether, MD, (winter 1990), the seroprevalence in women delivering in Durham County (North Carolina) in 1989 was higher. The increase in HIV seroprevalence in the midwest is a recent phenomenon, and the total number of infected children may consequently still be low. Furthermore, they would be less likely to have progressed to clinically apparent disease.

Another reason Dr Monteleone may have different results than ours is that patients were referred to Duke University Medical Center (Durham, NC) because they were HIV seropositive, not because they had been abused. The HIV-infected children in St Louis may be referred to a clinic other than his. Dr Monteleone does not say what proportion of his patients were tested initially for HIV or retested at the recommended interval. If he is relying on a history of an HIV-infected perpetrator or on symptoms of HIV infection to appear, he is not going to identify many of his patients who are HIV infected, since many HIV-infected patients may be asymptomatic for years.

Dr Monteleone commented that he has followed up four HIV-negative children who were abused by HIV-positive perpetrators. The type of

abuse (for example, penile-anal, fondling, etc) should certainly be specified. In addition, one of the many unresolved problems regarding sexual abuse of children is that the child's right to safety may conflict with perceived rights of the suspected perpetrator. In that regard, we also wonder whether Dr Monteleone has found a means of protecting other vulnerable children from abuse by the same perpetrators, and if so, how this was accomplished. A description of the experiences would be valuable.

Our data unequivocally demonstrate that there are children who are infected with HIV by sexual abuse, and that the number is substantial. There are significant limitations in the application of our data to a general population of abused children since the denominator in our study is children who are referred because they are HIV seropositive. To clarify this issue, Dr Gellert et al² have begun to gather badly needed data regarding acquisition of HIV through sexual abuse from child protection teams throughout the United States. At least 26 cases have been identified, including the four we reported. Any clinician who is evaluating children for sexual abuse should evaluate the child for HIV and other sexually transmitted diseases. Transmission does occur, so the problem is only going to get worse, and to deny that HIV transmission to children is a problem does a terrible disservice to those children who are HIV infected and in need of treatment for the infection and protection from further abuse.

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1. National HIV Seroprevalence Surveys: Summary of Results. DHHS publication HIV/CID 9-90/006. Atlanta, Ga: Centers for Disease Control; 1990.

2. Gellert G, Berkowitz C, Durfee M. Situational and sociodemographic characteristics of children infected with HIV from pediatric sexual abuse. Presented at the Seventh International Congress on AIDS; Florence, Italy. June 15-21, 1991.

Anal Fissure Produced by Examination for Sexual Abuse

Sir.—The article by Bays and Jenny¹ in the December 1990 issue of *AJDC* is a valuable review of the many physical findings that can be confused with sexual abuse. The authors stated that forceful abduction of the legs may cause splitting injuries of midline structures. I would like to report a case in which forceful abduction of the buttocks coupled with misrecognition of a normal structure led to a false assumption of sexual abuse.

Report of a Case.—A 12-month-old white girl was brought to the office by her mother. The mother gave a specific history that the father, who had only weekend custody, had had rectal intercourse with her daughter. The mother stated that the child had difficulty with bowel movements after a weekend visitation. The child had already been examined by an emergency department physician and another local pediatrician. Without prompting, the mother then suddenly demonstrated how the physicians examined her daughter by violently opposing the child's buttocks, thereby opening a large anal fissure. She also pointed out a bluish circumanal discoloration that she was told was a bruise. It was a venous plexus. Re-examination 5 days later showed healing of the anal fissure. The venous plexus was unchanged. Unfortunately, the mother remained convinced that abuse had occurred and the case remained open for several years.

Comment.—This case further illustrates that examinations performed by inadequately trained personnel may be more harmful than helpful. Current controversies over the effect of false allegations^{2,3} behoove us all to exercise great care and good judgment.

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1. Bays J, Jenny C. Genital and anal conditions confused with child sexual abuse trauma. *AJDC*. 1990;144:1319-1322.

2. Paradise JE, Rosatain AL, Nathanson M. Substitution of sexual abuse charges when parents dispute custody or visitation. *Pediatrics*. 1988;81:835-839.

3. Fay RE. Allegations of sexual abuse. *Pediatrics*. 1990;86:488-489.

In Reply.—The case described by Baker is unfortunate. It is intrusive and even abusive for a child to be taken to multiple examiners for repetitive genital examinations. Herman-Giddens and Berson¹ have described parents who focus excessively on their child's genitalia, including parents who performed genital inspections or took the child for multiple examinations or procedures by professionals. Many physicians have not been trained to perform detailed genital examinations,² and further confusion arises if the examiner is unsure or mistaken in interpreting physical findings. It is unfortunate that the mother in the case described by Baker, and apparently the child protective authorities, "remained convinced that abuse had occurred" even after being informed that the "bruise" was a venous plexus.

Regardless of whether a child is being molested, unresolved allegations of sexual abuse in the context of a divorce or custody dispute create additional stress for the child. These disputes can create an emotionally abusive atmosphere for the child. Ideally, the parents in such cases will agree to be counseled and focus on the welfare of their child.

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1. Herman-Giddens ME, Berson NL. Harmful genital care practices in children: a type of child abuse. *JAMA*. 1989;261:577-579.

2. Ladson S, Johnson CJ, Doty RE. Do physicians recognize sexual abuse? *AJDC*. 1987;141:411-415.

Gilding the Lily

Sir.—I am writing in regard to the Radiological Case of the Month on retropharyngeal abscess published in the December 1990 issue of *AJDC*.¹

Although Fig 2 of this article is a very nice exhibit of an abscess, I fail to see the necessity of computed tomography as part of the evaluation and treatment of a peritonsillar or retropharyngeal abscess. In the discussion, the computed tomographic scan adds little to the diagnosis or treatment. I can assure you, it adds much to the high cost of medical care.

The publication of such photos can be easily misinterpreted as a demonstration of the proper procedure in handling such cases. It is not. It is, in fact, an abuse of the available technology. It is abuses such as this that bring such strong reactions to control medical practice as a means of controlling medical costs.

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1. Grosso J, Myer CM, Wood BP. Retropharyngeal abscess. *AJDC*. 1990;144:1349-1350.

In Reply.—We certainly agree with Dr Faigel that in many situations there is

abuse of advanced technology in the form of "overtesting."

This particular infant, however, was suspected of having retropharyngeal abscess (RPA) several days before otolaryngologic consultation was obtained. A delay in treatment of an RPA leads to an increased risk that the infectious process may spread not only within the retropharyngeal space, but also to the parapharyngeal space, carotid sheath, and mediastinum. The surgical procedure for a complicated RPA is much different from that for an uncomplicated one. Most RPAs are incised and drained with a transoral approach. If there is spread of the abscess to the parapharyngeal space or within the retropharyngeal space below the hyoid bone, for example, an external neck approach is best.

As discussed in our article, a complete medical history, physical examination, and lateral neck roentgenography are the best tools for diagnosing an RPA. The computed tomographic scan, however, can delineate the extent of suspected spread of RPA, allowing the surgeon to plan the most appropriate surgical approach. Indeed, "overtesting" is not justified, but to reduce the morbidity and mortality associated with a disease process, such advanced technology should be used without hesitation.

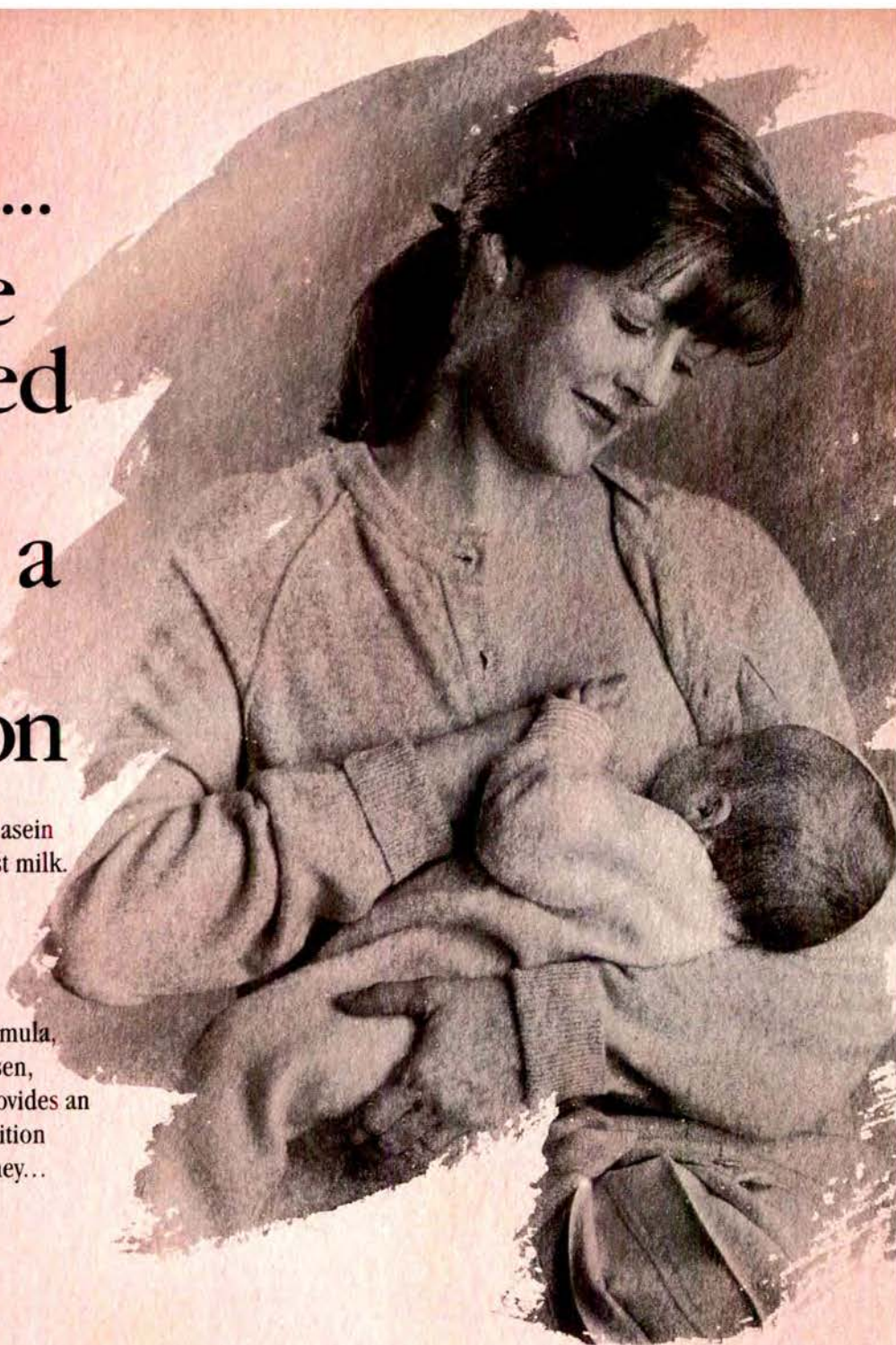
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Jack Metcoff Festschrift

In every field of endeavor, only a limited number of people make a major impact. Jack Metcoff has had such an influence in the fields of pediatric nephrology and body fluid physiology.

On June 11, 1990, a symposium and dinner was held in his honor. Several of the articles in this issue of the JOURNAL were presented at the symposium. Approximately 100 of his colleagues and students attended the event. Seventeen presented synopses of their experiences working with Dr Metcoff or their current research in pediatrics. Some of the presentations were submitted to and reviewed by *AJDC*, and those that were accepted appear in this issue.

Jack Metcoff was honored as an outstanding and visionary scientist, teacher, and leader. His scientific contributions include an early description of an experimental model of the nephrotic syndrome produced in the rat by injection of an aminonucleoside of puromycin and an elegant exposition of the mechanisms leading to development of the nephrotic syndrome and its renal dysfunction in that model. He also reported the early use of prednisone and diuretics for the treatment of the nephrotic syndrome in child-

hood. He was one of the first to use hemodialysis to treat renal failure in children, and his studies altered our understanding of renal function and fluid therapy after thermal injury. He was one of the first to integrate renal physiology and biochemistry and conducted multiple studies of renal metabolism. His international studies of protein-calorie malnutrition in pregnancy and renal failure have led to an improved understanding of the mechanisms that result in fetal malnutrition and to new approaches to therapy. In addition to his personal contributions to the scientific literature, he facilitated the growth of knowledge in pediatric nephrology by editing *The Annual Conference on the Kidney*. He was a catalyst and leader in the development and sustenance of the Nephrosis Foundation, which evolved into the National Kidney Foundation. The annual conferences on the kidney began in 1948 and concluded with a conference addressing acute glomerulonephritis in 1965. The proceedings of these conferences brought the cutting edge of the developing field of nephrology to the scientific and clinical community.

Many practicing pediatricians and pediatric academicians owe their initial stimulus and training to Jack Met-

coff. The most important quality, and the one for which I believe he would most want to be remembered, is his ability and ever-present desire to be a catalyst and supporter of young academicians. He has always regarded his most important role to be that of a facilitator and stimulator of ideas and people, and he gained great satisfaction from his students' successes. The articles in this issue reflect his influence on the fields of nutrition, metabolism, and nephrology. The fields of pediatric nephrology, fluid and electrolyte physiology, and clinical nutrition owe him great gratitude. He was usually ahead of his time, elevated socratic dialogue to a new level of excellence, and stimulated many students to enter a variety of disciplines in academic pediatrics or to practice primary pediatrics in the community with an ever-present quest for knowledge and the application of scientific principles to clinical problem solving.

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Part-time Peg: Who, Me?



Peggy C. Ferry, MD

Peggy has been a workhorse for AJDC. She has reviewed hundreds of manuscripts for us, suggested new features and procedures for AJDC, and recently implemented one of these, "Pediatric Legal Medicine." In addition, she has faithfully handled our "Book Review" section for the past 8 years. In her contribution this month, she details a change in professional life-style she has recently undergone. Having worked with Peggy during her full-time activities, I can attest to her dedication to hard work, to completion of all of her duties, no matter what she was asked to do, and to her professionally competent performance. I have no doubt that her "reduced" activity will not alter the way in which she performs, for academe and for AJDC. Even a brief glance at her curriculum vitae reveals continued high-level activity locally, regionally, and nationally. AJDC, pediatrics, and pediatric neurology have benefited from her energy, intelligence, and dedicated performance and will continue to do so, even if she is so-called part-time.

On a recent delightful sunny Arizona Saturday afternoon, I found myself seated next to a young visiting academic pediatrician who was being actively recruited to join our department. Sitting outside amidst the splendor of blue skies and

a Tucson mountain view, we discussed the rigors of academic pediatrics and the limited free time to spend with one's family. When I mentioned to the young man that I was thinking about writing an editorial on part-time work, he said, "Boy, I'd love to work part-time, but there's no way I could."

He is right. The vast majority of academic pediatric departments, as well as private practice groups, frown on hiring part-time physicians. It is almost as if they have a sign in the window: *Now Hiring—Full-Time Employees Only.*

In July 1989, after 30 years of virtually full-time practice (most of it in academic pediatric neurology), I stepped down from a full-time academic post (including associate headship of our department) and, for health reasons, began working part-time. I wrestled for a long time with the decision to make this change because I had always planned to work full-time until at least age 90 years or so. I had worked hard to achieve the professional successes for which I felt a reasonable degree of pride. Reducing my work schedule was not part of the vocabulary in my career trajectory.

I was unprepared for the reactions of my colleagues, most of whom developed a somewhat glazed look in their eyes when I told them I was going to work the "P" word (part-time). With one or two valued exceptions, they conveyed the opinion that I had dropped out of the mainstream of academic life and that my contributions were no longer valued. In retrospect, I think they were a bit jealous.

Their reactions stimulated me to think, however, about the role of part-time work in the future of pediatrics. Recently, a lot of publicity has been generated about "mommy-track" decisions that has brought needed public attention to different career tracks that competent women (and a few good men) will pursue in the years ahead. Prominent women in the public eye have spoken out forcefully on the issue, at the price of losing their jobs in some instances.

Barbara Bush also put it well in her address to the 1990 Wellesley graduating class: "At the end of your life, you will never regret not having passed one more test, winning one more verdict, or not closing one more deal. You will regret time not spent with a husband, a child, a friend, or a parent" (*Washington Post*, June 2, 1990:C4). In my own situation, my former husband is happily remarried to a tall, thin (sic!), younger woman; we decided years ago not to have children because it would interfere with our professional careers.

An astounding 62% of last year's PL-1s were women.¹ As noted in the title of a recent pithy *New England Journal of Medicine* editorial, "Medicine is no longer a man's profession: or, when the men's club goes coed, it's time to change the regs."² Change in the pediatric club is long overdue. The challenge to pediatric department chairpeople is clear: to attract and keep bright, competent women, academic units will need to modify their personnel policies accordingly. Otherwise, increasing numbers of these capable and caring individuals who wish to experience the joys of a good marriage, family life, and successful pediatric career will no longer enter the fast track because the price they would have to pay is too high. Successful major corporations, way ahead of the medical profession, have already learned this lesson by introducing flexible hours, extended leaves of absences, job sharing, and on-site child care. Pediatrics, of all fields, should exert leadership in academe to support issues regarding children and families, whether these children be ours, those we serve, or our colleagues'.

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2. Eisenberg C. Medicine is no longer a man's profession: or, when the men's club goes coed, it's time to change the regs. *N Engl J Med*. 1989;321:1542-1544.

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BRIEF SUMMARY:

DESCRIPTION: Septra (Trimethoprim and Sulfamethoxazole) is a synthetic antibacterial combination product.

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides. Patients with documented megaloblastic anemia due to folate deficiency. Pregnancy at term and during the nursing period, because sulfonamides pass the placenta and are excreted in the milk and may cause kernicterus. Infants less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA, OTHER BLOOD DYSCRASIAS AND HYPERSENSITIVITY OF THE RESPIRATORY TRACT.

SEPTRA SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice may be early indications of serious reactions. Cough, shortness of breath, and/or pulmonary infiltrates may be indicators of pulmonary hypersensitivity to sulfonamides. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Complete blood counts should be done frequently in patients receiving sulfonamides.

SEPTRA SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies have documented that patients with group A β -hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Septra than do those patients treated with penicillin, as evidenced by failure to eradicate this organism from the tonsillopharyngeal area.

PRECAUTIONS:

General: Septra should be given with caution to patients with impaired renal or hepatic function, to those with possible folate deficiency (e.g., the elderly, chronic alcoholics, patients receiving anticonvulsant therapy, patients with malabsorption syndrome, and patients in malnutrition states) and to those with severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

Use in the Elderly: There may be an increased risk of severe adverse reactions in elderly patients, particularly when complicating conditions exist, e.g., impaired kidney and/or liver function, or concomitant use of other drugs. Severe skin reactions, or generalized bone marrow suppression or a specific decrease in platelets (with or without purpura) are the most frequently reported severe adverse reactions in elderly patients. In those concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Appropriate dosage adjustments should be made for patients with impaired kidney function.

Use in the Treatment of *Pneumocystis carinii* Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): The incidence of side effects, particularly rash, fever, leukopenia, and elevated aminotransferase (transaminase) values with Septra therapy in AIDS patients who are being treated for *Pneumocystis carinii* pneumonia has been reported to be greatly increased compared with the incidence normally associated with the use of Septra in non-AIDS patients.

Information for Patients: See full product information.

Laboratory Tests: Complete blood counts should be done frequently in patients receiving Septra; if a significant reduction in the count of any formed blood element is noted, Septra should be discontinued. Urinalysis with careful

microscopic examination and renal function tests should be performed during therapy, particularly for those patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported.

It has been reported that Septra may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. This interaction should be kept in mind when Septra is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

Septra may inhibit the hepatic metabolism of phenytoin. Septra, given at a common clinical dosage, increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When administering these drugs concurrently, one should be alert for possible excessive phenytoin effect.

Sulfonamides can also displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: Septra, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs, however, if methotrexate is measured by a radioimmunoassay (RIA).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with Septra.

Mutagenesis: Bacterial mutagenic studies have not been performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels; at concentrations approximately 1000 times human plasma levels in these same cells a low level of chromosomal damage was induced at one of the laboratories.

Impairment of Fertility: No adverse effects on fertility or general reproductive performance were observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy: (See CONTRAINDICATIONS) Pregnancy Category C. In rats, oral doses of 533 mg/kg sulfamethoxazole or 200 mg/kg trimethoprim produced teratological effects manifested mainly as cleft palates. The highest dose which did not cause cleft palates in rats was 512 mg/kg sulfamethoxazole or 192 mg/kg trimethoprim when administered separately. In two studies in rats, no teratology was observed when 512 mg/kg of sulfamethoxazole was used in combination with 128 mg/kg of trimethoprim. In one study, however, cleft palates were observed in one litter out of 9 when 355 mg/kg of sulfamethoxazole was used in combination with 88 mg/kg of trimethoprim. In some rabbit studies, an overall increase in fetal loss (dead and resorbed and malformed conceptuses) was associated with doses of trimethoprim 6 times the human therapeutic dose.

Nursing Mothers: See CONTRAINDICATIONS.

Pediatric Use: See CONTRAINDICATIONS.

ADVERSE REACTIONS: The most common adverse effects are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). (See WARNINGS section.) For more information on adverse reactions, see full product information.

OVERDOSAGE: See full product information.

PLEASE CONSULT FULL PRODUCT INFORMATION BEFORE PRESCRIBING.

Zinc Deficiency

A Public Health Problem?

Harold H. Sandstead, MD

• Zinc deficiency occurs in individuals and populations whose diets are low in sources of readily bioavailable zinc such as red meat, and high in unrefined cereals that are rich in phytate and dietary fibers. Dietary zinc deficiency was described nearly three decades ago among the poor of the Middle East. It is now known to occur in children and adolescents from widely diverse areas including Egypt, Iran, Turkey, China, Yugoslavia, Canada, and the United States; and among pregnant women from Iran, Turkey, the United Kingdom, Australia, and the United States. Major manifestations include retarded growth and development and an increased incidence of pregnancy complications. Other manifestations may include suppressed immunity, poor healing, dermatitis, and impairments in neuropsychological functions. Precise information as to the numbers of people affected by dietary zinc deficiency is not available. Even so the nature of diets associated with zinc deficiency suggests that mild deficiency is common in some populations.

(AJDC. 1991;145:853-859)

The first unequivocal evidence of primary human zinc deficiency was reported by Prasad et al,^{1,2} who studied adolescent Egyptian village boys. Subsequently, in 1967, the improved growth and sexual maturation of the boys following zinc treatment were described.³ Coincident with the studies in Egypt, Halsted et al⁴ investigated the syndrome in growth-stunted adolescents from Iranian farm villages. They found that both boys and girls were affected. They also conducted controlled therapeutic trials of zinc in village schoolboys and showed that their growth improved subsequent to zinc repletion.

See also pp 860, 865, 871 and 877.

Adolescents with the Prasad-Halsted syndrome display severe growth retardation, delayed sexual maturation, and in most instances, iron deficiency (Figure). Plasma zinc levels are generally reduced. Measurements of zinc kinetics are

consistent with zinc deficiency in that isotopic tracers of zinc given intravenously rapidly disappear from the plasma, and their retention in the body is prolonged.² Treatment with zinc and an adequate intake of other nutrients stimulated linear growth, maturation of the skeleton, and development of the genitalia and secondary sex organs to a greater extent than treatment with diet alone or diet and iron.^{3,4}

From an examination of the settings in which the Prasad-Halsted syndrome occurs, it appears that the affected individuals represent index cases of a common problem among the poor. The syndrome is associated with poverty and the consumption of diets that include large amounts of unleavened whole-meal wheat bread, a rich source of phytate. Red meat and other sources of highly bioavailable zinc are infrequently consumed. In Egypt, blood loss from hookworm and schistosomiasis infections causes further impairment of zinc nutriture. In Iran, geophagia is a common practice among village children. Clay forms insoluble complexes with iron.⁵ Presumably, it also binds zinc and inhibits its absorption.

The discovery of dietary zinc deficiency in humans provided substantial stimulation to study the role of zinc in metabolism, human physiology, and disease. Before that time, the essentiality of zinc for plants⁶ and experimental^{7,8} and farm animals^{9,10} had been established, and the impairment of zinc utilization by dietary phytate had been described in chicks.¹¹

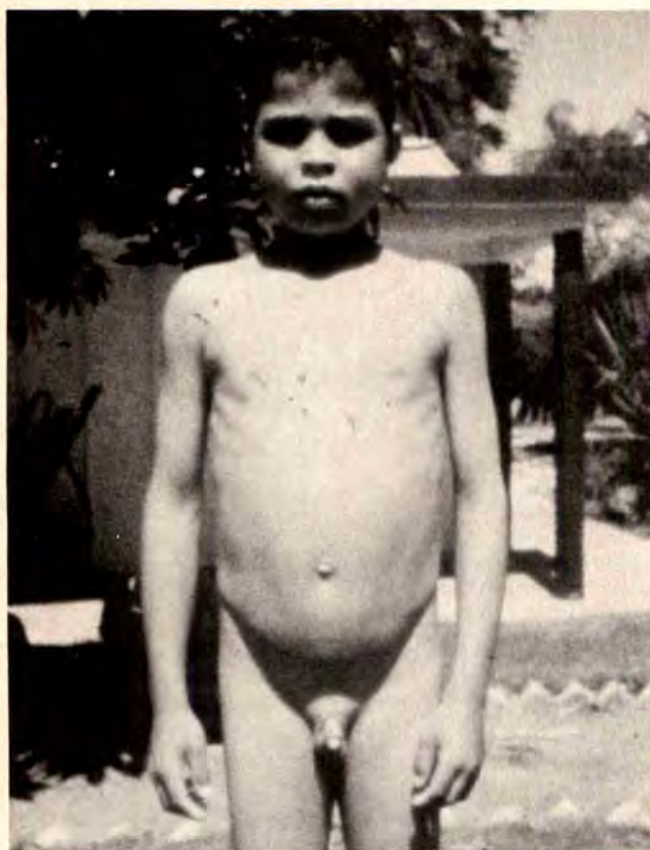
The following and many other studies established the essentiality of zinc for cell growth and differentiation. Lieberman et al¹² were among the first to show that zinc is essential for synthesis of DNA by mammalian cells. They found that the activity of DNA polymerase was reduced in zinc-deprived kidney cells in vitro. Subsequent in vivo research disclosed that the synthesis of DNA, RNA, and proteins was suppressed in zinc-deficient rats to a greater extent than in pair-fed control rats.¹³⁻¹⁷ Similarly, zinc deficiency was found to cause reductions in activities of some enzymes that mediate these processes. Examples include thymidine kinase,¹⁸ DNA-dependent RNA polymerase,¹⁶ and aminoacyl-tRNA synthetase.¹⁹ Other studies found fewer polysomes on sucrose-density gradients of brain and liver from zinc-deficient rats than control rats.^{20,21} More recently the binding of zinc to strategically located cysteines and histidines in the peptide chain of auxiliary transcription factors was reported. Factor IIIA of *Xenopus laevis* was the first of those "finger proteins" to be recog-

Accepted for publication February 11, 1991.

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Presented at the Jack Metcalf Festschrift, Chicago, Ill, June 11, 1990.

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Sixteen-year-old zinc-deficient Egyptian boy with a prepubertal physical appearance and growth stunting. This subject was studied at US Naval Medical Research Unit 3 in Cairo, Egypt, in 1963.³

nized.²² Other findings suggest that zinc mediates enzymes that degrade nucleic acids. The activity of ribonuclease is increased in tissues from zinc-deficient animals,²³ while the activity of nucleoside phosphorylase is depressed by zinc deficiency.²⁴ Further information on zinc deficiency can be found in reviews.²⁵⁻²⁷

Factors in the pathogenesis of primary zinc deficiency include the zinc content of the diet, the consumption of dietary and other substances that affect zinc bioavailability, and the homeostatic capacity of the individual to retain zinc. The zinc content of foods varies widely, as does its bioavailability. The zinc content of commonly consumed food in the United States is indicated in Table 1.²⁸ Current data²⁹ suggest that about 50% of zinc in US diets is provided by meat, and that beef is the principle source.³⁰ Dairy products provide about 20%, while cereals and legumes provide most of the remainder. In contrast to omnivorous diets, most of the zinc in lacto-ovo-vegetarian diets is provided by cereal products (26%), beans and nuts (26%), and milk and eggs (18%).³¹

A variety of substances in the diet can affect the bioavailability of zinc. Inhibitors include phytate (hexaphosphate inositol), oxalate, certain components of dietary fiber, products of Maillard browning, phosphopeptide products of the digestion of casein, ferrous iron, calcium, copper, and cadmium.³²⁻³⁷ Facilitators include digestible dietary proteins, histidine, cysteine, citrate, picolinate, and ethylenediaminetetraacetic acid.³⁸⁻⁴¹

Phytate is believed by many investigators to be the most important dietary inhibitor of zinc bioavailability. It is present in many food products that are derived from

Table 1.—Zinc Content of Common Household Portions of Selected Foods

Food	Portion	Zinc, mg	Protein, g
Fish (flounder, tuna, salmon)	3 oz	0.58	22.89
Oysters	3 oz	77.51	6.00
Crab	3 oz	6.48	16.46
Poultry			
Dark meat	3 oz	2.20	22.08
Light meat	3 oz	0.87	25.34
Beef	3 oz	4.60	26.82
Pork	3 oz	4.40	26.72
Bologna	3 oz	1.70	13.02
Liver (chicken, beef, pork)	3 oz	4.90	23.48
Whole egg	1 large	0.70	6.07
Dried beans and lentils	½ cup	0.95	7.70
Milk	1 cup	0.93	8.03
Cheese (cheddar)	1 oz	0.88	7.05
Bread			
White	1 slice	0.15	2.07
Wheat	1 slice	0.47	2.69
Rice			
White	½ cup	0.35	2.00
Brown	½ cup	0.60	1.80
Cornmeal (cooked)	½ cup	0.15	1.50
Oatmeal (cooked)	½ cup	0.58	3.00
Bran flakes (40%)	1 oz	1.16	3.20
Corn flakes	1 oz	0.03	0.95

*Source: United States Department of Agriculture; Agricultural Handbooks, 1976-1988.

plants. Whole grain cereals and legumes are the major sources of phytate for humans. The inhibitory effects of phytate and calcium on zinc nutrition were first described in chicks and rats.^{11,42} It is now known that phytate complexes with zinc and calcium together at alkaline pH to form highly insoluble compounds.³⁵ The inhibition of human zinc absorption by phytate was suggested by the findings of Reinhold et al,⁴³ in which diets rich in phytate lowered zinc retention. Subsequent zinc tolerance tests in humans confirmed that foods rich in phytate reduce zinc absorption.⁴⁴ More recently, Turnland et al⁴⁵ showed that sodium-phytate suppresses the retention of stable isotopic tracers of zinc by humans.

Semiquantitative studies by Sandström et al⁴⁶ indicate that retention of zinc is inversely related to the level of dietary phytate. They fed subjects 80-g meals of rye, barley, oatmeal, triticale, or whole wheat that were labeled with zinc 65 and measured retention of the isotope 14 days later using whole-body counting technology. The retention of zinc was inversely proportional to the amount of phytate present in the meal. For example, an intake of 600 µmol of phytate was associated with a retention of 8%, while a phytate intake of 100 µmol was associated with a retention of 25%. These investigators had previously shown that 16 hours of leavening caused a substantial reduction in phytate in whole-wheat bread and a doubling of zinc 65 retention from a standard meal.⁴⁷ Sandström et al⁴⁸ also found that the impact of phytate from beans on zinc retention was less than that of

Table 2.—Factorial Basis of Provisional Requirements of Dietary Zinc in Assumed Losses and Availability*

Age	Peak Daily Retention, mg	Urinary Excretion, mg	Sweat Excretion, mg	Total Required, mg	Daily Dietary Requirement as a Function of Available Zinc, mg		
					10%	20%	40%
Infants, mo							
0-4	0.35	0.4	0.5	1.25	12.5	6.3	3.1
5-12	0.2	0.4	0.5	1.1	11.0	5.5	2.8
Boys, y							
1-10	0.2	0.4	1.0	1.6	16.0	8.0	4.0
11-17	0.8	0.5	1.5	2.8	28.0	14.0	7.0
≥18	0.2	0.5	1.5	2.2	22.0	11.0	5.5
Girls, y							
1-9	0.15	0.4	1.0	1.55	15.5	7.8	3.9
10-13	0.65	0.5	1.5	2.65	26.5	13.3	6.6
14-16	0.2	0.5	1.5	2.2	22.0	11.0	5.5
≥17	0.2	0.5	1.5	2.2	22.0	11.0	5.5
Pregnant women, wk of gestation							
0-20	0.55	0.5	1.5	2.55	25.5	12.8	6.4
20-30	0.9	0.5	1.5	2.9	29.0	14.5	7.3
30-40	1.0	0.5	1.5	3.0	30.0	15.0	7.5
Lactating women	3.45	0.5	1.5	5.45	54.5	27.3	13.7

*The above estimates are based on the assumption that the fat-free tissue concentration of zinc in man is approximately 30 µg/g. This figure is equivalent to 2.0 g of zinc in the soft tissues of an adult male and 1.2 g in the soft tissues of an adult female, as determined from lean body mass. The zinc requirement at various ages was determined from the change in lean body mass with age. Bone zinc was not included in these calculations, because it is relatively sequestered from the metabolically active pool of body zinc. The excretion of zinc in sweat is based on an assumed zinc content in sweat of 1 mg/L. The estimated requirement for lactation is based on a zinc content in milk of 5 mg/L and a daily milk secretion of 650 mL. The urinary excretions of zinc are based on levels reported.⁴³

phytate from cereal products.

The effects of relatively small intakes of wheat bran on zinc retention were shown by balance studies in which 20 normal men were fed 26 g of wheat bran daily as part of a mixed diet of conventional North American foods.⁴⁹ Zinc retention was measured in intervals of 26 to 30 days. The phytate content of the control diet was 0.29 mmol daily compared with 1.42 mmol daily in the experimental diets. Analysis of covariance, with dietary zinc as the covariate, revealed that zinc retention was reduced substantially ($P < .01$) when wheat bran was included in the diet. Regression analysis of data from 195 similar balance studies found that dietary phytate, calcium, nitrogen, and zinc were significant ($P < .05$) predictors of zinc retention. Together they accounted for 20% ($P < .0001$) of the variance in zinc retention.

Findings from a study by Solomons et al⁵⁰ support the thesis that the inhibition of zinc retention by phytate and other zinc-binding substances in foods that are commonly consumed by the poor can be severe. Solomons et al measured the increase in plasma zinc in humans after meals of oyster, oyster with beans, and oyster with tortilla. Plasma zinc rose substantially after a meal of 120 g of oyster. When 120 g of beans were fed with the oyster, the increase in plasma zinc was reduced by more than 50%. When 120 g of tortilla were fed with the oyster the increase in plasma zinc was almost completely suppressed. Thus, absorption of highly bioavailable zinc was impaired by two foods that are important constituents of diet of the poor throughout Central and South America.

Findings by Brune et al⁵¹ indicate that humans do not adapt to habitually high intakes of phytate. Using the absorption of iron 59 from a standard meal as an index, they found that vegetarians experienced as much inhibition of iron absorption by wheat bran as did nonvegetarians. These findings indicate that it is unlikely that the poor of

less developed countries adapt to the high phytate contents of their habitual diets.

Reinhold et al³² pointed out that components of dietary fiber can also inhibit the intestinal absorption of zinc by humans. A zinc 65 tracer study by Lykken et al⁵² in normal volunteers showed that increased consumption of Maillard browning products in corn flakes can reduce retention of zinc, as measured by whole-body counting of the retained isotope.

Thus, it seems clear that a number of binding substances present in foods can reduce zinc retention. Their negative impact on human zinc nutriture becomes apparent when they are eaten in large amounts, as occurs when humans depend primarily on whole-grain cereal products for their subsistence.

Factorial estimates of human zinc requirements and their relation to bioavailability are shown in Table 2.⁵³ For example, a 10-year-old child requiring 1.6 mg of zinc daily for growth and tissue maintenance needs to consume 4.0 mg of zinc daily if the dietary zinc is 40% bioavailable. On the other hand, if the zinc is only 10% bioavailable, an intake of 16 mg daily would be needed. From this it is apparent that food choice and food availability must have a major impact on zinc nutriture. Restricted food choices appeared to be a key factor in the pathogenesis of the Prasad-Halsted syndrome. Because of this, Waslien⁵⁴ evaluated diets of poor Egyptian village families for zinc content and the sources of zinc. She found that the average intake was 8 mg daily and that 71% was provided by bread and other cereal products while meat, poultry, and fish provided about 6%. Sandström et al,⁵⁵ as part of a recent World Health Organization committee, calculated zinc requirements similar to those in Table 2. They estimated that less than 10% to 15% of the zinc is bioavailable from diets such as those described by Waslien. In contrast, the sources, content, and bioavailability of zinc from North

Table 3.—Zinc Intakes in Diets of Children, Adults, and Vegetarians

Age	Sex	No. of Subjects	Mean \pm SD Zinc Intake, mg/d*	Population†	Source, y
1 mo	M/F	35	1.90 \pm 0.20	Breast-fed, Canada	McDonald et al, ⁹⁰ 1982
1 mo	M/F	25	3.60 \pm 0.60	Bottle-fed, Canada	McDonald et al, ⁹⁰ 1982
6 mo	M/F	16	2.70 \pm 0.50	Breast-fed, Canada	McDonald et al, ⁹⁰ 1982
6 mo	M/F	23	4.60 \pm 0.70	Bottle-fed, Canada	McDonald et al, ⁹⁰ 1982
2-7 y	M/F	96	6.30 \pm 0.44	Middle income, US	Hambridge et al, ⁷² 1979
2-6 y	M/F	85	5.00*	Low income, US	Walravens et al, ⁶⁴ 1983
3-5 y	M/F	5	6.36 \pm 0.83	Norwegian children	Schlage and Wortberg, ⁹¹ 1972
10-13 y	M/F	6	10.16 \pm 1.42	Norwegian preteens	Schlage and Wortberg, ⁹¹ 1972
14-16 y	F	15	12.00 \pm 5.00	High school, US	White, ⁵⁶ 1969
18-30 y	F	21	13.80 \pm 7.27	College women, US	White, ⁵⁶ 1969
14-64 y	M/F	22	8.60 \pm 0.52	Middle income, US	Holden et al, ⁵⁷ 1979
30 y	F	100	10.10 \pm 3.30	Canadians, omnivorous	Gibson and Seythes, ⁵⁸ 1982
Adult	F	5	6.40 \pm 1.69	Vegetarians, US	King et al, ⁹² 1981
Adult	M	5	20.30 \pm 8.80	Military, US	Milne et al, ⁹³ 1980
81.7 y	M/F	21	5.53	Geriatric hospital	Thomas et al, ⁹⁴ 1988
85.5 y	M/F	24	8.90 \pm 2.53	Healthy elderly	Bunker et al, ⁹⁵ 1984
25-48 y	M/F	112	8.50 \pm 4.50	Vegetarians, Punjabi, Canada	Bindra et al, ⁹⁶ 1986

*No readings were reported for entries with no SD values.

†Diet assessment was as follows: via 3-day records taken at home visits in breast- and bottle-fed Canadians; 24-hour recall and food checklists in middle- and low-income US subjects; 2-week food records in Norwegian children and preteens; weighed 24-hour diets with duplicate food composite in US female and high school subjects; 14-day food record and 132 diet composites in middle-income US subjects aged 14 to 64 years; 3-day food records and 24-hour food composite in omnivorous Canadians; 3-day food records in US vegetarians; 6 days of duplicate chemical diet composites in US military subjects; duplicate chemical diet composites in geriatric hospital subjects and the healthy elderly; and 3-day weighed records and 30 1-day duplicate composites in vegetarian Punjabi Canadians.

American mixed omnivorous diets is substantially higher. For example, a study of 21 US college women (Table 3) who ate self-selected cafeteria diets found a mean (\pm SD) of 13.8 \pm 7.3 mg of zinc consumed daily.⁵⁶ Another study of 22 middle-income men and women found that their home diets provided 8.6 \pm 0.1 mg zinc daily.⁵⁷ A study of 100 Canadian women found a zinc intake of 10.1 \pm 3.5 mg daily.⁵⁸ As noted previously, about 50% of the zinc in omnivorous mixed North American diets is provided by meat.³⁰ The availability of zinc from such diets is probably 20% to 30%.⁵⁵ This level of bioavailability will allow a dietary intake of about 12 mg to be fully adequate for adult men who consume an omnivorous mixed western diet.^{53,55}

Since its discovery three decades ago, dietary zinc deficiency has been described among children of many countries. Turkish workers⁵⁹ found zinc and iron deficiencies in growth-stunted children who indulged in geophagia. Subsequently, Chinese investigators reported evidence that led them to speculate that 30% of Chinese children are stunted from zinc deficiency.⁶⁰ In a study of 187 children they found that hair zinc and relative height for age were related ($P<.002$). They treated 50 growth-retarded children with 1.2 to 2.0 mg of zinc per kilogram per day and found that their growth rate was 40% greater than that of 235 normal children who were not given zinc ($P<.001$). A study from Yugoslavia⁶¹ of 110 children aged 9 to 12 years found strong associations of relative body height and hair with plasma zinc ($r=.95$ and $.93$, respectively). More recently 70% of schoolchildren from northeastern Thai villages were reported to have low plasma zinc.⁶²

The first description of dietary zinc deficiency in the United States was reported from Denver, Colo, in 1972.⁶³ Hambridge et al⁶³ found short stature, low weight, and poor appetite in preschool infants and children that were associated with low levels of zinc in hair. Treatment of the chil-

dren with zinc improved their appetites and growth. More recently, growth retardation associated with low zinc nutrition was found by Walravens et al⁶⁴ among poor Hispanic preschool children from Denver. Treatment with zinc improved growth. A recent survey of the US population found a 3.3% \pm 0.91% (SE) incidence of low serum zinc ($<10.7 \mu\text{mol/L}$) in children aged 3 to 8 years, irrespective of income.⁶⁵ Stature and serum zinc were not associated, perhaps because serum zinc can be perfectly normal in mild zinc deficiency.^{63,64,66} In Canada, Gibson et al⁶⁶ found an association between short stature in young boys and low levels of hair zinc. Treatment with zinc improved their growth. These investigators⁶⁷ had previously reported associations between hair zinc levels and short stature in 13 boys. All had hair zinc levels of less than the 70 ng/g found in 48 boys of more normal stature ($P<.05$). They ascribed the lower hair zinc levels in the growth-stunted boys to poor food choices. Dietary histories indicated that they consumed 15% less meat, poultry, and fish ($P<.01$), and more fluid milk ($P<.05$), than the control group.

Information on diets and requirements suggests that children with zinc intakes in the lowest quartile are at risk of zinc deficiency. Balance studies found that intakes of 7 to 8 mg of dietary zinc in a mixed omnivorous diet allowed young children to absorb 2.1 to 3.4 mg daily.^{68,69} In contrast, the data of Price et al⁷⁰ indicate that 7- to 10-year-old girls fed diets similar to those consumed by low-income children in the Southeastern United States were in negative zinc balance when the diet provided about 4.6 mg of zinc and 25 g of protein daily and the estimated losses of zinc in sweat were included in the balance calculation.⁷¹ When the zinc intake was increased to 6.8 mg and the protein intake to 46 g daily, the retention of zinc was positive.

According to surveys conducted by the United States Department of Agriculture,²⁹ the average zinc intake of US

children is about 7.5 mg. Studies cited in Table 3 by Hambridge et al⁷² and Walravens et al⁶⁴ found that mean (\pm SD) zinc intakes of 96 middle-income and 85 low-income children aged 2 to 7 years and 2 to 6 years, respectively, from the Denver area were 6.30 ± 0.44 mg and 5.00 ± 0.35 mg (assuming a similar coefficient of variation as the middle income group). Calculations of the zinc intakes of children who were 1 SD below the mean indicates zinc levels of 5.86 and 4.65 mg, respectively. At 20% absorption, this provides about 1.17 and 0.93 mg of zinc, respectively, amounts below the factorially estimated World Health Organization^{53,55} requirement of 1.5 to 1.6 mg daily.

Pregnant women are another group at risk of zinc deficiency.⁷¹ Factorial estimates of zinc requirements of pregnant women⁷¹ suggest that pregnant women should retain about 400 μ g of zinc daily in the second trimester and 750 μ g of zinc during the third trimester. An evaluation of the reported zinc contents of self-selected diets of young women suggested that 20% to 30% of the subjects would have been at risk of zinc deficiency if they had been pregnant and the bioavailability of the zinc from their diets was 20%.⁷¹ In a 1976 study from Sweden⁷³ of about 300 pregnant women, abnormal pregnancy outcomes were associated with low plasma levels of zinc in the first trimester.

Experimental studies in animals have revealed that zinc nutriture is particularly critical during pregnancy.^{14,74-79} In chickens and rats, zinc deficiency retards growth and maturation of the blastula, embryo, and fetus. Death of concepti and a variety of malformations occur. Parturition is impaired and perinatal survival reduced. Surviving offspring display residual behavioral abnormalities.

The hypothesis that zinc deficiency during human pregnancy is an important problem in the Middle East was put forward by Sever and Emanuel.⁸⁰ They based their hypothesis on knowledge of the effects of zinc deficiency on pregnant animals and the clinical evidence of zinc deficiency among adolescents from Egypt and Iran. They proposed that endemic zinc deficiency among the poor is the cause of the high rates of neural tube defects among Middle Eastern babies. A report from Turkey of low levels of zinc in plasma of women who delivered anencephalic infants⁸¹ supports Sever and Emanuel's suggestion.

Evidence consistent with the occurrence of zinc deficiency among pregnant women in the United States was provided by a 1984 report that described associations between low maternal plasma zinc levels in the second and third trimester and subsequent pregnancy complications in 394 women from Ohio.⁸² Data analysis by z scores indicated that more complications occurred in women with plasma zinc levels in the lowest quartile than in women with plasma zinc in the highest quartile ($n = 89$, $P < .02$). Fetal distress was more frequent among women with plasma zinc levels in the lowest than the highest quartile ($n = 33$, $P < .002$). Step-wise discriminant analysis revealed that zinc, albumin, and transferrin were important discriminators for complications in the lowest quartile plasma zinc sub-population, and that zinc was not a discriminator in any other quartile. Associations between complications of pregnancy and plasma zinc were unique to the lowest quartile.

Evidence that maternal zinc nutriture has a profound effect on human fetal growth was provided by Meadows et al.⁸³ Using the concentration of zinc in a preparation that contained peripheral blood maternal leukocytes as an index of zinc status, they found that severe fetal growth failure was more common in women who, at term, had low levels of zinc

in the cellular isolate. They also found that the level of zinc in the cellular isolate was highly correlated with the level of zinc in maternal muscle. Consistent with this association between low maternal tissue zinc and fetal growth failure were the findings by Favier et al⁸⁴ of an association between baby size and the zinc concentration in amniotic fluid.

The frequency with which zinc deficiency occurs in human pregnancy is uncertain. Jameson et al⁸⁵ found a 17.5% incidence of plasma zinc level of less than 10 mmol/L in 1231 Swedish women who attended a maternity clinic before the eleventh week of pregnancy. A recent study of 460 low-income women in Alabama reported that lowest quartile plasma zinc levels in the first trimester were associated with a likelihood of subsequent delivery of an infant weighing less than 2500 g that was eight times that associated with highest quartile plasma zinc levels.⁸⁶ Maternal plasma zinc at 16 weeks' gestation, adjusted for dilution, was directly related to infant birth weight ($r = 0.32$, $P < .001$).

The cause-and-effect relationship between maternal zinc nutriture and pregnancy outcome has been studied in a randomized controlled trial.⁸⁷ In 295 normal-weight, primiparous, low-income, pregnant teenagers from New Orleans, La, zinc treatment (30 mg daily) reduced the rate of premature delivery by 32% ($P < .05$) and nearly eliminated the need for respiratory assistance of newborns ($P < .002$). Jameson⁸⁸ previously described 133 women with plasma zinc levels of less than 10 mmol/L at 14 weeks' gestation, of whom 64 were given zinc and 69 were given placebo. Sixty-three percent of the women given zinc delivered normally and had normal infants. In contrast, 50% of the women given placebo had complications. Further study of 1231 women given zinc or placebo showed a significant ($P < .01$) reduction in the incidence of perinatal death in the zinc-treated group compared with the placebo-treated group.⁸⁵ It should be noted that the beneficial effects of zinc treatment on pregnancy outcome were less evident in a study of Mexican-American women.⁸⁹ This study did not evaluate the response to treatment in terms of the underlying nutritional status of the subjects, as was done in the study from New Orleans. This might account for the limited evidence of treatment benefit.

In summary, the available evidence supports the hypothesis that zinc deficiency is an important public health problem both internationally and domestically. Estimates of human zinc requirements at different times in the life cycle,^{53,55,71} the zinc content of human diets,^{28,54} and evidence that phytate and other factors can impair the utilization of dietary zinc^{28,33,36,46,49} suggest that the risk of zinc deficiency increases as economic resources and the availability of a varied diet decrease. Clinical zinc deficiency among infants, children, adolescents, and pregnant women has been described both in developing countries and industrialized countries, including the United States. These clinical examples are believed to represent index cases of a more widespread problem whose true extent is presently unknown. Experiments in humans and animal models have established the essential role of zinc in many physiologic functions, including immunity, taste acuity, dark adaptation, wound healing, lipid metabolism, sexual function, and cognition.^{25,26} It is unclear how frequently these manifestations of zinc deficiency occur in humans. This issue needs clarification.

There is a need to define the prevalence of and the factors that cause human zinc deficiency more precisely. Randomized controlled trials of zinc treatment in growth-retarded infants and children and in pregnant women in

populations where stunting and abnormal pregnancy outcomes are prevalent would be useful. Data from such research would provide a basis for health authorities to institute preventive measures.

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Paleonephrology and Reflux Nephropathy

From the 'Big Bang' to End-Stage Renal Disease

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• Urinary tract infections, in association with ureteral reflux or dysperistalsis, may lead to invasive renal parenchymal infection and residual scarring (reflux nephropathy). Such infections in infants are often not diagnosed during the acute phase. Late sequelae of reflux nephropathy include hypertension, proteinuria, or chronic renal failure. The latter may eventuate in the subset of patients with urinary tract infection and unilateral reflux extending to a solitary kidney or bilateral reflux. Proteinuria may herald the inexorable progression of glomerular sclerosis in patients destined to progress to end-stage renal disease, despite the absence of further recurrences of urinary tract infections. The mechanism of progression is probably similar to that occurring in other forms of chronic, diffuse parenchymal renal disease, which all have similar alterations in glomerular hemodynamics (an increase in glomerular capillary flow, pressure, and filtration). The consequent hyperfiltration per nephron may be related to the level of dietary protein intake or to some derivative of the protein load. Hyperfiltration appears to recapitulate the presumed renal hemodynamic response to the relatively high level of episodic meat consumption by paleolithic hunter-gatherers. A prudent therapeutic intervention in children with progressive reflux nephropathy may be a proportional reduction in protein intake.

(AJDC. 1991;145:860-864)

The most common cause of end-stage renal disease (ESRD) in children and young adults is reflux neph-

See also pp 853, 865, 871, and 877.

ropathy.¹ Although other morbidities, such as hypertension² or the Ask-Upmark kidney,³ are associated with reflux nephropathy, the main focus of this review is the

mechanism that causes a disease occurring for the first time during infancy to progress inexorably, in some individuals, to ESRD many years later.

URINARY TRACT INFECTIONS (UTIs), THE 'BIG BANG,' AND REFLUX NEPHROPATHY

Urinary tract infections in infants and children are commonly encountered in clinical practice. Although UTI can occur at any age, infections in young infants are especially of concern. The consensus among pediatric nephrologists is that the very first UTI in a vulnerable infant may be sufficient to cause permanent renal scarring. This vulnerability results from mechanisms for extension of infection from the lower urinary tract to the renal parenchyma. Although the resulting invasive renal infection is often referred to as "acute pyelonephritis," a more accurate term is "acute infective interstitial nephritis."

Two principal mechanisms lead to invasive renal infection: vesicoureteric reflux extending to the renal pelvis, and, in children without demonstrable reflux, ureteral dysperistalsis.⁴ The latter is facilitated by a unique host-microbial interaction, which involves the attachment of certain organisms, with specific molecular groupings on their surfaces, to complementary receptors on uroepithelial cells. In particular, certain P-fimbriated strains of *Escherichia coli* have been implicated.⁵ Local inflammation of the ureter may impair peristalsis, further contributing to urinary stasis. Imaging studies have shown a relationship between infection with such "pyelonephritogenic" strains of *E coli* and increased ureteral width.⁶ Moreover, microbial adherence presumably allows pathogens to resist the "washout" effect of urinary flow and facilitates retrograde migration toward the kidneys.

Other host factors predisposing to focal renal scarring as a consequence of parenchymal infection include the occurrence of compound papillae and their association with intrarenal reflux.⁷ Herein, renal scarring is referred to as reflux nephropathy, although it is recognized that some scars may follow UTI in the absence of reflux. Jacobson et al⁸ have proposed the term "postinfectious focal renal scarring" as an alternative to reflux nephropathy.

The notion that the very first UTI can inflict permanent renal scarring has been referred to as the "big bang" theory.^{7,9} According to this theory, only one infection in an infant or young child with ureteral reflux or dysperistalsis

Accepted for publication February 4, 1991.

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Presented at the Festschrift for Jack Metcalf, MD, Chicago, Ill, June 11, 1990.

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is sufficient to lead to scarring. Often, the first UTI is not recognized as such but has been misdiagnosed as "fever of unknown origin."

Recognition that substantial renal damage can occur in the absence of further recurrences of infection suggests that UTIs, in certain vulnerable infants, are not benign. In particular, infants with reflux extending to a solitary kidney, or bilateral high-grade reflux, are especially vulnerable to serious long-term sequelae, including ESRD.

A recent report suggested that chronic renal disease may be a more likely outcome than is generally appreciated. An extended follow-up (average, 27 years) of young adults with a history of a febrile UTI as infants and children, demonstrable renal scars on intravenous urograms, and a high prevalence of reflux in the subset studied with voiding cystograms showed that all patients had evidence of chronic renal disease.⁸ Ten percent of the group already had progressed to ESRD.

THE MECHANISM OF PROGRESSION TO CHRONIC RENAL FAILURE

It is known that progression to ESRD can occur in the absence of further occurrences of UTI and despite surgical correction of reflux.¹⁰ It is now believed that the mechanism of progression of reflux nephropathy to ESRD involves the same "final common pathway" as in other forms of diffuse renal parenchymal disease.

The "nephron hyperfiltration" hypothesis of Brenner et al¹¹ has been invoked as an explanation for an irreversible, progressive course. Considerable data suggest that the loss of a "critical mass" of functioning nephron units, or glomerular capillary surface area,¹² in the face of an unchanged excretory load initiates an increase in glomerular capillary flow and pressure, resulting in hyperfiltration by remnant glomeruli. The nature of endogenous vasoactive substances responsible for an increase in glomerular capillary blood flow and pressure is unknown, although it is believed that the effector substance causes a preferential increase in constrictive tone of the efferent arteriole, facilitating an increase in single-nephron glomerular filtration rate. The role of locally released vasoactive hormones is currently under study.¹³ The precise stimulus to hyperfiltration is also unknown. Certain amino acids or humoral factors, such as glucagon, have been implicated.¹⁰

Hyperfiltration, if sustained, is injurious and leads, in some unknown way, to expansion of mesangial matrix and progressive glomerular sclerosis. As individual nephron units are rendered nonfunctional, the cycle becomes self-perpetuating. The mesangial injury, coupled with hyperfiltration, causes alterations in glomerular permselectivity, culminating in pathologic proteinuria. Microalbuminuria has been observed to correlate with increasingly severe renal scarring in children with reflux nephropathy.¹⁴ The point in time at which this cycle of progressive disease becomes irreversible appears to correspond to a decline of renal excretory function to less than 50% of normal.¹⁵ The emergence of nephrotic-range proteinuria is ominous and marks the development of glomerular sclerosis,¹⁶ which progresses in parallel with the underlying initial interstitial renal disease. The pathologic term often used for the end-stage kidney of reflux nephropathy is "chronic atrophic pyelonephritis," which, however, fails to reflect the superimposed lesion of glomerular sclerosis.

Although renal hyperechogenicity on ultrasound examination is a nonspecific finding,¹⁷ recent reports of a diffuse

or nodular ("pseudotumoral") hyperechoic pattern have suggested a marker for the detection of hyperfiltration.^{18,19}

Nephron hyperfiltration, if viewed teleologically as a compensatory response to an altered excretory load per nephron, makes physiologic sense. Nevertheless, sustained hyperfiltration, by producing disease, is counterproductive and is considered a "disorder of adaptation."²⁰ The precise relationship of hyperfiltration to the development of focal sclerosis is not fully understood. As mentioned above, Brenner et al¹¹ have proposed that hyperfiltration results in mesangial injury, perhaps related to an increase in transcapillary flux of macromolecules, which, in some unknown way, leads to sclerosis. Other data suggest that the key development is glomerular hypertrophy and altered growth dynamics of infiltrating or resident glomerular cells.^{21,22} However, the latter mechanism may not be independent from glomerular hypertension as a risk factor for the development of progressive disease.²³

Nevertheless, in view of the pathogenic potential of hyperfiltration, further questions arise: Why does a mechanism for hyperfiltration even exist? Was there once a survival advantage for such a mechanism? There is evidence that the evolutionary basis of hyperfiltration may lie in the food-procurement behavior of our ancestors.

PALEONEPHROLOGY

The paleolithic period of human evolution encompasses 2 million years, beginning with fabrication of rudimentary stone tools by our hominid ancestor, *Homo habilis*, and ending with the emergence of agriculture, between 5000 and 10 000 years ago. Approximately 40 000 years ago, biologically modern humans emerged (*Homo sapiens sapiens*), and during the ensuing period, brain size and the human genetic pool are believed to have changed little. Until about 10 000 years ago, it is estimated that the diet of our hunter-gatherer forebears consisted of a large proportion of meat obtained by hunting or carcass scavenging.²⁴ According to Brenner et al,¹¹ the capacity to hyperfilter was salutary for our primitive ancestors, who lived during epochs when the food supply was marginal. Until the relatively recent advent of settled human societies with knowledge of farming (some 8000 to 10 000 years ago), there were some 30 000 years of a marginal existence for hunter-gatherers. During much of this period, the planet was in the grip of the last glaciation, and the climate was colder. The expanding human population probably did not migrate beyond subtropical latitudes, increasing competition for the food supply. Survival depended on hunting ability, both for nutritional sustenance and animal skins for warmth. Reproductive success may also have depended on hunting ability; the successful hunter was more likely to mate with a receptive female.²⁵

Success as a hunter depended on physical strength, at least for predation of large animals. The requisite physical strength, in turn, mandated sufficient protein intake to maintain muscle mass. A successful hunt of large game depended on a close approach to an animal. The hunter, using a spear, then had to lunge with considerable thrust to mortally injure the animal. The imperative to maintain muscle mass is consistent with evidence that the paleolithic diet consisted of a high proportion of animal protein, probably derived from large grazing animals.²⁴ Despite the abundance of vegetation in the tropical savannas that supported herds of grazing animals, the supply of edible

Renal Solute Load of Late Paleolithic Humans*

Solute	Load, mmol (or mOsm)/d
Ureat	1487
Sodium	30
Potassium	285
Ammonium†	70
Anions‡	385
Total	2257

*Based on estimates of dietary intake of late paleolithic humans (10 000 to 40 000 years ago) by Eaton and Konner.²⁴ The renal solute load for a 70-kg human is 32 mOsm/kg per day.

†Urea derived from the daily dietary protein intake of 251.1 g,²⁴ assuming zero net nitrogen balance.

‡Assuming net hydrogen ion excretion as ammonium to be 1.0 mmol/kg per day and ignoring net acid excretion as titratable acid.

§Assuming 1:1 cation-anion equivalence (a slight overestimate, as this assumption ignores the minor effect of divalent anions).

plants was probably meager, and hunting of large mammals persisted as the major means of food procurement.²⁶

A successful hunt yielding sufficient meat for the clan was probably not accomplished on a daily basis. It is likely that the animal protein intake of the clan oscillated between "feast" and "famine." During several successive days of limited food intake, demands on renal excretory function would have been minimal, and glomerular filtration would have declined to a "resting" level,¹¹ perhaps analogous to the low filtration rate now observed in chronic malnutrition.²⁷ On the day of a successful hunt, the clan gorged themselves. Consequently, there was a sudden need to modulate renal glomerular hemodynamics in support of a glomerular filtration rate commensurate with the excretory load of urea and electrolytes.

Based on the assumption that the diet of hunter-gatherers contained 35% meat, the nutrient composition²⁴ and the renal solute load can be estimated (Table). The paleolithic meat eater had a relatively high potassium intake relative to sodium. Moreover, the overall renal solute load was relatively high (32 mOsm/kg per day).

The estimates of the paleolithic diet²⁴ are based on the assumption of a readily available food supply in terms of predation on a day-to-day basis. Given an alternative assumption that the availability of big game on a day-to-day basis was marginal and that consumption of meat occurred on an intermittent basis with binge-type meals, the consequent solute and potassium load presented an enormous excretory challenge to the kidneys. Thus, the intermittent nature of food intake of our ancestors resulted in the gradual evolutionary development of a mechanism for up- and down-regulation of intraglomerular hemodynamics, especially the filtration rate. In essence, nephron hyperfiltration, evolving over tens of thousands of years of intermittent intake and binge-eating, was an appropriate adaptation to conditions of precarious nutrition at the time. This vestigial primitive reflex became encoded in the genetic memory of our species. Thus, reflex glomerular hyperfiltration to a protein meal persists to this day.^{28,29}

After the last glacial retreat, beginning 14 000 years ago,³⁰ and as the climate became more hospitable and grazing animals migrated to latitudes formerly covered by ice, primitive human societies were less preoccupied with mere survival. Between 8000 and 10 000 years ago, humans learned to plant seed, cultivate wheat, and raise livestock for milk, meat, blood, and, in the instance of sheep, wool for clothing. Thus, the transition from hunter-gatherer to farmer-herder marked the beginning of some

degree of control over the food supply, favoring more frequent meals. According to Bronowski,³¹ the signal event in the meteoric ascent of human civilization was a genetic mutation (a tripling of the chromosome complement) of a species of wild grass, leading to the evolution of wheat. The seeds of this mutant, instead of being scattered by the wind, had to be manually collected and sowed. Thus, the emergence of farming lessened dependence on big-game hunting, and, for the first time, grain became an important component of the diet. Humans were now able to provide meals for themselves more frequently, although the effects of climatic events on the availability of food probably continued to impose a considerable degree of episodicity on meals.

After the emergence of the Bronze Age, tools and weapons were more efficient, and hunting strategies, including trapping and stampeding, became more refined. Because there was now less of a need for brute strength for the purpose of hunting, coupled with the development of agriculture, humans began to consume less animal protein. In fact, this transition was apparently accompanied by a decline in stature (of about 15 cm) compared with the height of the hunter-gatherer.²⁴ Because humans were now able to provide meals for themselves on a regular, frequent basis, it is likely that the average level of glomerular perfusion reached a higher "set point" to cope with frequent, repeated excretory loads.

The most important electrolyte accompanying a high-protein meat meal, consumed in raw form along with animal blood erythrocytes, is potassium. If the glomerular filtration rate were not appropriately up-regulated from the resting state, dangerous hyperkalemia after a binge meal might have ensued. Because urea, the major excretory product of protein metabolism in humans, is not directly toxic, it is tempting to speculate that hyperfiltration evolved as an adaptation to the most compelling excretory challenge of protein intake: the rapid elimination of potassium. Because hyperfiltration probably results in increased distal delivery of sodium, which provides the sodium necessary for exchange with secreted potassium, it may serve as the first line of defense against an acute potassium load. In the face of a sustained potassium load, the regulatory loop is completed by stimulating renin release, ultimately leading to increased aldosterone secretion. Given the relatively low sodium content of the paleolithic diet (Table), the dual imperatives of sodium conservation and potassium elimination are perfectly conjoined by means of aldosterone-regulated distal sodium-potassium exchange. In fact, according to one view, the renin-angiotensin-aldosterone mechanism primarily functions as a defense against potassium excess.³² Remarkably, a recent review does not cite data as to the pure effect of an acute potassium load on whole-kidney or single-nephron glomerular filtration rate.³³ The hypothesis that the artifice of hyperfiltration evolved as an adaptation to cope with intermittent binge eating and, in particular, the imperative to eliminate potassium remains speculative.

The critical balance of excretory load and renal mass is changed in renal disease. Although the absolute excretory load is in the usual range, the nephron complement, reduced by disease, is now burdened with an increased load per nephron. The primitive reflex of renal glomerular hyperfiltration is activated. Thus, for some infants and young children with UTI and renal scarring, the progression to

ESRD many years later is a recapitulation of an evolutionary adaptation to the binge-meal, meat-eating dietary habits of our paleolithic ancestors.

IMPLICATIONS OF PALEONEPHROLOGY FOR PEDIATRIC PRACTICE

The central biologic process of infant and child health is growth. The level of protein intake is a critical determinant of optimal growth. Current recommendations of infant nutrition have resulted in levels of protein intake commensurate with that ingested naturally by means of breast-feeding. One can only speculate whether higher levels of protein intake by infants during the era that non-humanized milk formula was widely used had adverse renal effects, perhaps subtly in the form of glomerular sclerosis. It is known that a gradual process of glomerular senescence attends the aging process. It is possible that this process is not normal or physiologic but reflects the sustained high level of excretory demands on the kidney throughout one's life.³⁴

Focal glomerular sclerosis culminating in chronic renal failure has been reported in children with a single kidney.³⁵ A recent case report documented focal glomerular sclerosis in a child with a solitary kidney affected by oligomeganephronia and a supernormal creatinine clearance.³⁶ Studies in adults with a single kidney since childhood have shown a gradual decline in renal excretory function from a baseline of higher-than-expected values and the emergence of microalbuminuria.³⁷ The question arises: Should children with a solitary kidney due to congenital absence, disease, or trauma of the contralateral kidney or surgical removal have a reduction in dietary protein intake? A definitive answer is not currently available, but a proportional reduction of protein intake may be prudent if a collaborative study currently in progress yields data supporting such intervention.³⁸

A common recommendation in the management of the nephrotic syndrome in children is to increase the dietary intake of protein as compensation for urinary losses of albumin. Is it possible that "supernormal" glomerular filtration rates observed in some nephrotic children³⁹ and the common pathologic lesion of focal glomerular sclerosis are consequences of high exogenous protein intake or augmented endogenous protein synthesis by the liver? Is the development of focal sclerosis related to renal vasodilatory effects of glucocorticoids?⁴⁰

Should children known to have chronic renal disease, including those with reflux nephropathy, have dietary limitations imposed early in life? If protein restriction is employed, is there a concomitant risk of impaired somatic growth?⁴¹ If data emerge supporting the salutary effect of dietary protein restriction, the possible impairment of growth may be a reasonable tradeoff for a delay in the progression to ESRD. Preliminary data suggest that dietary protein restriction lessens urinary protein excretion in children with reflux nephropathy.¹⁴

The implications of diet modification for patients with chronic renal disease are so far reaching in terms of the enormous demand currently for ESRD treatment that a multicenter, collaborative study of protein and phosphorus limitation is currently in progress.³⁸ Although the efficacy of therapeutic strategies aimed at interdicting the development of sustained hyperfiltration and progressive glomerular sclerosis is controversial,^{42,43} recent studies suggest that protein restriction may be beneficial.⁴⁴⁻⁴⁶ A

feasibility study of dietary protein restriction in infants with chronic renal insufficiency has yielded preliminary data.⁴⁷

Because angiotensin-converting enzyme inhibitors have a predominant effect on the glomerular efferent arteriole, the possible benefit of such agents in the amelioration of progressive renal disease has been considered.⁴⁸ A short-term study involving children, most of whom had primary glomerular diseases, showed that therapy with angiotensin-converting enzyme inhibitors was efficacious in reducing proteinuria.⁴⁹ The long-term benefit of such pharmacotherapy remains to be established.

The question of the possible risk of focal glomerular sclerosis in the remaining kidney of individuals donating a kidney has been raised.¹⁰ Although follow-up studies generally show stable renal function, available preliminary data suggest that some donors may develop proteinuria, microalbuminuria, or hypertension.⁵⁰⁻⁵⁵ If long-term follow-up indicates a substantial risk to kidney donors, transplant programs will have the ethical obligation to inform prospective donors of such risks.

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X-linked Hypophosphatemia

Genetic and Clinical Correlates

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● X-linked hypophosphatemia is a hereditary form of rickets that results from an isolated renal tubular wasting of phosphate. The clinical features unique to this disorder, and the recent advances in our understanding of vitamin D metabolism and molecular genetics in X-linked hypophosphatemia are reviewed. Finally, a succinct critique of the controversial treatment modalities round up this review.

(AJDC. 1991;145:865-870)

X-linked hypophosphatemia, previously regarded as a rare disease, is the most frequent cause of familial rickets, with an incidence of one in 20 000 births.¹ This disorder is an isolated phosphate transport defect at the renal tubule that is inherited by X-linked dominant trans

See also pp 853, 860, 871, and 877.

mission and characterized clinically by hypophosphatemia, growth retardation, and rickets, most pronounced in male patients.² It has been repeatedly demonstrated that the degree of hypophosphatemia is not correlated to the severity of skeletal lesions,³⁻⁵ which supports the suggestion of an associated primary defect in the osteoblasts⁶ in patients with X-linked hypophosphatemia as well as in the Hyp mouse, the murine homologue of the human disease. As the affected patient ages, osteomalacic bone pain, pseudofractures, skeletal deformities, progressive ankylosis, and dental caries occur.⁷ Herein, we review the progress made in the last decade concerning both biochemical and genetic aspects of this disease and examine the strengths and weaknesses of new treatment modalities with vitamin D metabolites, phosphate, and diuretics. The use of magnetic resonance spectroscopy in a clinical setting to study intracellular phosphate metabolism, the evidence of an as yet unidentified phosphaturic factor as suggested by parabiosis experimentation, and a review of the powerful tools of molecular genetics with the potential to identify the gene defect in this disorder will form the final focus of our report.

Accepted for publication January 24, 1991.

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TREATMENT REGIMENS

As recently as 1980, the standard therapy for X-linked hypophosphatemia consisted of high doses of vitamin D₂ (10 000 to 50 000 U/d) and phosphate supplementation (1.5 to 2.0 g/d in five divided doses) to maintain the serum phosphate concentration above 1 mmol/L. Hypercalcemia, a frequent complication associated with high doses of vitamin D₂, was often prolonged because of the ongoing storage of vitamin D₂ in adipocytes. Consequently, constant concerns among physicians who treat these patients⁸ are the complications of hypercalcemia, hypercalciuria, nephrocalcinosis, and nephrolithiasis, some or all of which are associated with progressive deterioration of renal function.

Despite earlier reports^{9,10} of a lack of response to 1,25-dihydroxyvitamin D₃, Hirschman et al¹¹ reasoned that there must be a defect in the regulation of 1 α -hydroxylase in X-linked hypophosphatemia and proved their hypothesis in 1978 by treating an affected child with pharmacological doses of 1,25-dihydroxyvitamin D₃, thereby reversing rickets and growth retardation. Concurrent and subsequent studies¹²⁻¹⁵ in the early 1980s continued to confirm these initial observations. In addition, intensive efforts by a number of investigators in the mid-1980s substantiated this 1 α -hydroxylase defect in humans¹⁶⁻¹⁹ as well as in the Hyp mouse, the murine homologue of the human disease.^{20,21}

The principal therapy for X-linked hypophosphatemia is phosphate supplementation in five or more daily doses to compensate for the renal phosphate wasting. However, phosphate supplementation alone is often associated with secondary hyperparathyroidism,^{22,23} especially in patients with low concentrations of circulating 1,25-dihydroxyvitamin D₃. These advances in our understanding of disordered vitamin D metabolism in X-linked hypophosphatemia provide the rationale for the use of pharmacologic doses of 1,25-dihydroxyvitamin D₃ in the treatment of this disease. The initial clinical impression²² in 1980 that 1,25-dihydroxyvitamin D₃ was superior to vitamin D₂ or 25-hydroxyvitamin D₃ (Fig 1) received unequivocal support in 1990 when a clinical trial²³ of almost a decade's duration involving 40 patients demonstrated that 1 α -hydroxyvitamin D₃ (1 to 3 μ g/d) promoted substantial improvement in linear growth when compared with treatment with 25-hydroxyvitamin D₃ (50 to 200 μ g/d) or vitamin D₂ (0.5 to 2 mg/d). Each of these treatment

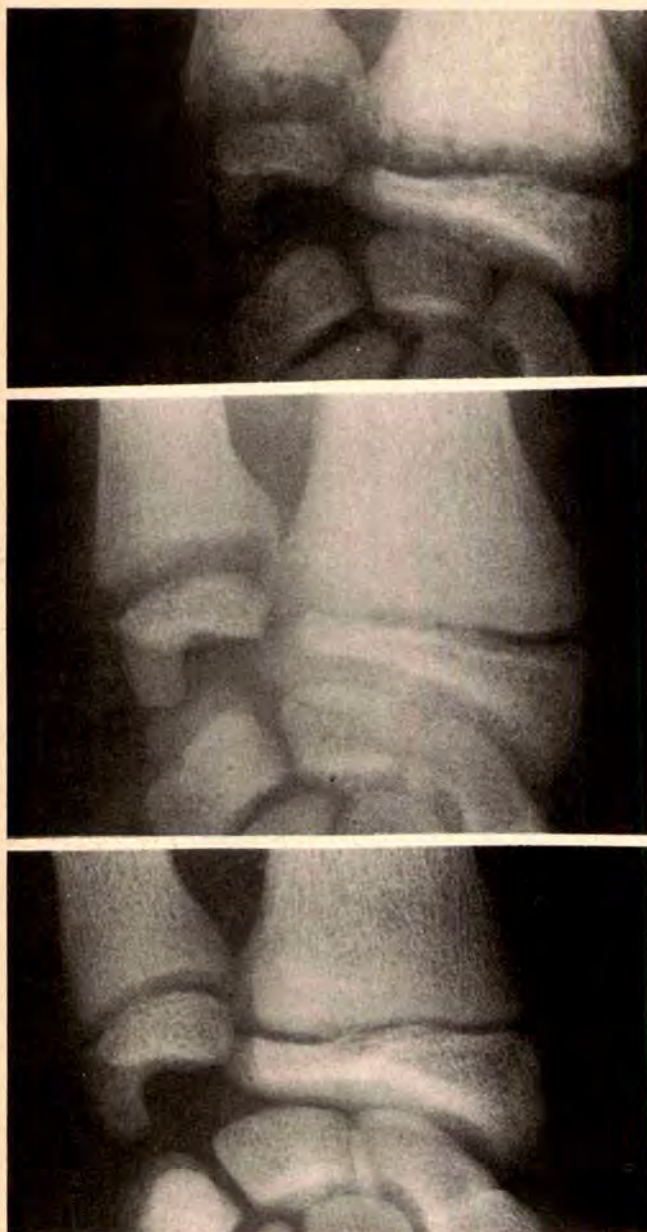


Fig 1.—Roentgenograms of the wrist in a child with X-linked hypophosphatemia. Top, Rickets present at age 14 years, after 7 years of treatment with phosphate supplementation (up to 2000 to 4000 mg/d) and vitamin D₂ (40 000 to 60 000 U/d), including an 8-month period when 25-hydroxyvitamin D₃ was administered. These therapeutic measures were insufficient to heal rickets. Middle, Marked healing of rickets 6 months after replacement of 25-hydroxyvitamin D₃ treatment with 1,25-dihydroxyvitamin D₃ treatment. Note substantial narrowing of the epiphyseal plate and reduction of flaring. Bottom, Complete healing after 12 months of treatment with 1,25-dihydroxyvitamin D₃ plus continued phosphate supplementation (from Chan et al²²).

regimens was coupled with oral phosphate supplementation (0.7 to 2.1 g/d in four or five divided doses). According to this clinical trial by Balsan and Tieder,²³ 75% of the 1 α -hydroxyvitamin D₃- and phosphate-treated group achieved normal stature, with accelerated and catch-up growth occurring primarily between the age of 2 years and puberty; this is in distinct contrast to the lack of response

in the majority of those treated with vitamin D₂ or in the group treated with 25-hydroxyvitamin D₃ plus phosphate. These provocative observations can be interpreted in several ways. The effectiveness of 1 α -hydroxyvitamin D₃ is unlikely due to more effective bone healing because radiologic findings were found to be similar among the three treatment groups. It is possible that pharmacologic dosages of vitamin D₂ and 25-hydroxyvitamin D₃ have a more toxic effect than does 1 α -hydroxyvitamin D₃ on the growth of chondrocytes. Alternatively, 1 α -hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ may directly and specifically enhance growth plate and chondrocyte multiplication.

In addition, whereas rickets are controlled with phosphate supplementations and vitamin D₂, endosteal bone lesions are controlled only with phosphate supplementation and 1,25-dihydroxyvitamin D₃. It is hypothesized that pharmacologic doses of 1,25-dihydroxyvitamin D₃ are needed to overcome the bone resistance. The fact that vitamin D₂ in pharmacologic doses fails to increase 1,25-dihydroxyvitamin D₃ concentrations has been taken as further support of this hypothesis.⁸

Hypercalcemia and hypercalciuria were encountered by a number of patients²⁴ following the administration of 1,25-dihydroxyvitamin D₃ at dosages of 30 to 40 ng/kg per day plus phosphate supplementation, the dosage required to maintain normal serum phosphate concentrations. However, on reducing the dosage of 1,25-dihydroxyvitamin D₃, radiologic evidence of bone lesions was again observed. In this subset of patients, the addition of a diuretic regimen to contract the extracellular volume, to enhance tubular reabsorption of phosphate, and to reduce urinary calcium excretion²⁴ has permitted an adequate dosage of 1,25-dihydroxyvitamin D₃ to promote bone healing without hypokalemia, metabolic alkalosis, and other observable side effects. The recommended diuretic regimen consists of hydrochlorothiazide and amiloride hydrochloride.²⁵ The latter medication is a potassium-sparing diuretic that prevents the hypokalemic metabolic alkalosis sometimes encountered with the use of hydrochlorothiazide alone.

The current recommendations for the treatment of X-linked hypophosphatemia can be summarized as follows: (1) 1,25-dihydroxyvitamin D₃, calcitriol (Rocaltrol, 0.25 μ g or 0.5 μ g per capsule), in an initial dose of 15 to 20 ng/kg per day with subsequent increases to 30 to 60 ng/kg per day during several months to achieve a maintenance serum phosphate concentration of at least 1 mmol/L. It should be noted that the dosage of 1,25-dihydroxyvitamin D₃ should be modified upward according to the severity of the rickets and the growth velocity. Hypercalciuria prevents the use of higher doses of 1,25-dihydroxyvitamin D₃. During the first 5 years of life and during puberty, the dosage is usually higher on a per-kilogram—body weight basis. The dosage is usually lower in patients 5 to 12 years of age. (2) Phosphate salts (Neutro-Phos, 1000 mg per 300 mL, or four capsules) to supply a total dose of 2000 to 4000 mg of phosphate per day in five to six divided doses until bedtime. The phosphate supplements are begun in small doses (30 to 40 mg/kg per day in five to six divided doses) to alleviate the gastrointestinal side effects of nausea and diarrhea. The dose is increased over several months to maintain the serum phosphate concentration at or above 1 mmol/L. (3) Patients are monitored with monthly serum calcium

and phosphorus determinations as well as urine calcium/creatinine ratios. A urinary calcium/creatinine (both in milligrams per deciliter) ratio above 0.25 is indicative of hypercalciuria. When this is encountered, the dosages of calcitriol must be decreased or phosphate supplementation increased, or hydrochlorothiazide and amiloride must be added. The two diuretics are in a 5:1 proportion, with the initial dose of hydrochlorothiazide at 1.5 to 2.5 mg/d and amiloride at 0.3 to 0.5 mg/kg per day.

To evaluate the bone status, roentgenograms of the hands, wrists, ankles, and knees should be obtained every 1 to 3 years. To evaluate the risk of nephrocalcinosis, a renal ultrasound²⁶ scan is obtained every 12 months. To avoid the risk of hyperparathyroidism that is occasionally encountered due to phosphate supplementation without the suppressive effects of concomitant 1,25-dihydroxyvitamin D₃ administration, intact (1-84) parathyroid hormone concentrations should be determined semiannually or yearly. To assess the effect of treatment on linear growth, the patients' heights should be measured annually. For the sporadic cases, the heights of the parents should be obtained for the midparental height calculations,²⁷ to provide an estimation of the target height for the treated patients. It is difficult to use the midparental heights in the familial cases, because the final height of the affected parent is determined by the success of treatment.

In the 1990s and beyond, the powerful tools of molecular biology will surely reveal the gene defect and eventually lead the way to gene therapy, which will be the definitive treatment. In the meantime, the wider availability of recombinant human growth hormone may lead to a new therapeutic approach.²⁸ The rationale for this belief is that exogenous growth hormone can promote tubular reabsorption of phosphate alone or in conjunction with 1,25-dihydroxyvitamin D₃ plus phosphate treatments and can promote normalization of serum phosphate, healing of the rachitic process, and acceleration of linear growth, while avoiding some of the treatment-related complications currently being encountered.

TREATMENT COMPLICATIONS

The treatment of X-linked hypophosphatemia, in the past with pharmacologic doses of vitamin D₂, 25-hydroxyvitamin D₃ plus phosphate supplementation and more recently with 1,25-dihydroxyvitamin D₃ plus phosphate supplementation has been fraught with controversy. While low-dose vitamin D treatment regimens have little chance of reversing the rachitic and osteomalacic processes or preventing dental caries and osteoarthritis, high-dose treatment regimens increase the risk of hypercalcemia, hypercalciuria, and renal damage.²⁹⁻³²

The initial ultrasonographic demonstration of nephrocalcinosis in treated children with this disorder by Alon et al²⁶ in 1983 led to later documentation in 1987 by Goodyer et al³⁰ that 47% of a large series of children with this disorder treated with 1,25-dihydroxyvitamin D₃ had evidence of nephrocalcinosis. Such a high risk of potential kidney damage has given rise to the contention that children with X-linked hypophosphatemia should never be treated at all³³; in a retrospective study that lasted almost 50 years, the final adult heights of untreated patients were not significantly different from those of the treated patients.³³ Furthermore, in an earlier report, Stickler et al³⁴ demonstrated that the treated affected twin suffered pseudofractures, whereas the untreated affected twin es-

caped this complication of X-linked hypophosphatemia. However, the intense efforts by a number of investigative teams in the past decade have clearly demonstrated a 1 α -hydroxylase defect in both X-linked hypophosphatemic humans and mice.¹⁷⁻²¹ Finally, the extensive studies by Hardy et al⁷ and Reid et al³⁵ in 1989 of a large series of affected adults further demonstrate the high prevalence of the progressive ankylosis of the spine and major joints, dental caries, pseudofractures, and other complications in the essentially untreated patients. Based on the strength of such data, most physicians are unwilling to subscribe to the provocative suggestion to withhold treatment from affected patients.

Several lines of evidence³⁶⁻⁴¹ suggest that 1,25-dihydroxyvitamin D₃ directly suppresses parathyroid hormone secretion and that the use of phosphate alone leads to continuous stimulation of the parathyroid glands, resulting in hyperparathyroidism. To avoid this complication, Alon et al²⁹ recommended that when hypercalcemia or hypercalciuria is encountered, vitamin D and phosphate supplements should be simultaneously withheld until normal calcium values are reestablished. The continued administration of phosphate supplements as before, while withholding 1,25-dihydroxyvitamin D₃ because of hypercalcemia, is no longer tenable in light of the current understanding of the parathyroid suppressive effects of 1,25-dihydroxyvitamin D₃.³²⁻³⁷

MAGNETIC RESONANCE SPECTROSCOPY AND MUSCLE PHOSPHORUS

X-linked hypophosphatemia has reportedly been distinguished from all other forms of hypophosphatemia by the absence of muscle weakness.⁴² Inorganic phosphate, a substrate in the formation of high-energy phosphate compounds, is used by muscle in anaerobic and aerobic metabolism. It also acts to modulate the kinetic rates of several key enzymes in metabolism. In view of the universal finding of a reduced serum phosphate concentration associated with this disorder, a disturbance of intracellular inorganic phosphate concentration and metabolism is also likely in X-linked hypophosphatemia. With the use of magnetic resonance spectroscopy (Fig 2), Clarke et al⁴³ demonstrated a subnormal concentration of intramyocellular inorganic phosphate in five patients with X-linked hypophosphatemia compared with those of five age- and sex-matched control subjects. Furthermore, intramyocellular phosphate concentrations increased within 24 hours in patients after initiation of standard 1,25-dihydroxyvitamin D₃ therapy without phosphate supplementation (Fig 2). These results contrast with those of Smith et al⁴⁴ in four adult female patients in whom intracellular phosphate concentrations were normal, which could account for the preservation of muscle strength despite severe systemic hypophosphatemia. However, there is no evidence to indicate an active transport mechanism, specific to the myocytes of X-linked hypophosphatemia, to maintain intracellular phosphate values greater than serum values. Therefore, previously reported data⁴³ are more in agreement with those reported in magnetic resonance spectroscopy studies of other forms of chronic hypophosphatemia and are consistent with the current understanding of disordered vitamin D metabolism in this disease.

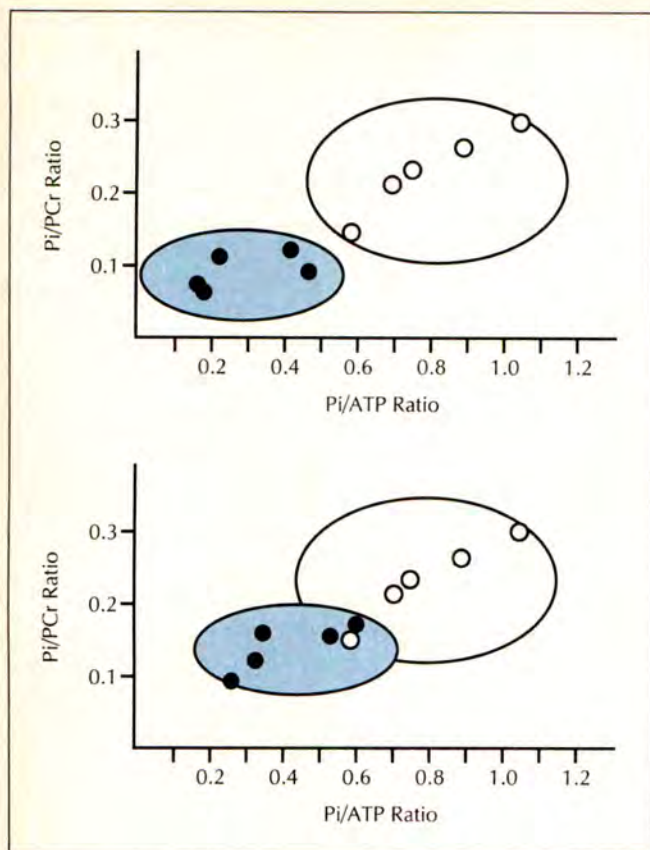


Fig 2.—Ratio of intracellular phosphate (Pi) to phosphocreatine (PCr) concentrations before and after treatment with 1,25-dihydroxy-vitamin D₃ in X-linked hypophosphatemia compared with that of age- and sex-matched control subjects. Scatterplots depict the Pi/PCr ratio vs the Pi to adenosine triphosphate (Pi/ATP) ratio measured for each patient (solid symbols) and control subjects (open circles). The ellipses are centered at the mean value for each group and their semiaxes are ± 2 SDs from the mean. Top, Control group compared with patients not receiving medication. Bottom, Control group compared with patients receiving medication. Data are from Clarke et al.⁴³

PARABIOSIS IN THE HYP MOUSE

Meyer et al^{45,46} recently demonstrated a humoral factor, unrelated to parathyroid hormone, in the development of phosphate wasting in the Hyp mouse. Within 3 weeks of parabiotic union through the peritoneal space between a Hyp mouse and a normal mouse, renal phosphate wasting and hypophosphatemia were documented in the normal mouse (Fig 3). After separation of the parabiotic union, the renal phosphate wasting ceased and normophosphatemia was restored in the normal mice.

In studies of the brushborder membrane vesicles of the normal mouse joined by parabiosis with the Hyp mouse,⁴⁵ a defective phosphate transport was demonstrated, again attesting to the transfer of a humoral substance to cause hyperphosphaturia in the normal animals. It is unlikely that parathyroid hormone is unlikely the cause of the phosphaturia, because parathyroidectomy did not affect the phosphate transport defect. Glucose uptake in brushborder membrane vesicles was unaffected by genotype or parabiosis. These studies point to the possibility of a humoral factor other than parathyroid hormone to account for the hypophosphatemia in the Hyp mouse.

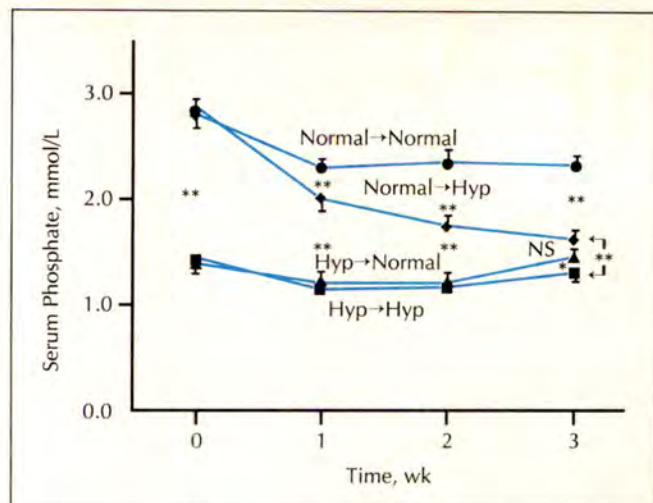


Fig 3.—Parabiosis experiment in Hyp mice and normal mice. Note the substantial hypophosphatemia in the normal mice after 3 weeks of parabiosis with the Hyp mice. Double asterisks indicate $P < .01$; single asterisk, $P < .05$. These are significant differences compared with the values above and below the symbols. NS indicates not significant. Data are from Meyer et al.⁴⁵

ADVANCES IN MOLECULAR GENETICS

In the last decade, illuminating molecular genetic research in the Hyp mouse,⁴⁷ the murine homologue of the human disease, stimulated Reade et al⁴⁸ and Machler et al⁴⁹ in 1986 to localize the human hypophosphatemic gene to the distal end of the X-chromosome at the Xp22 region or band.

The building blocks of DNA are called nucleotides. Each DNA nucleotide includes one sugar-phosphate backbone and one base. The 100 restriction enzymes currently available can cut the double-stranded DNA molecule into fragments at specific recognition sites consisting of specific base pair sequences. Each restriction enzyme cuts the DNA molecule at each site where the specific base pair sequence appears. The resulting DNA fragments, after exposure to a specific restriction enzyme, can vary in length. These variations in the length ("polymorphism") between recognition sites are inherited in a mendelian fashion.⁵⁰ Molecular genetics has taken advantage of this restriction fragment length polymorphism to test whether a particular gene defect may also be inherited together with the same fragment. Linking these DNA fragments to a gene defect within a large family narrows the search to a fragment of the 6 million base pairs in human DNA. The probes most often linked to an affected family provide a better idea of the location of the gene defect.⁵¹ Such statistical analysis of linkage is vastly enhanced by special computer programs and the availability of large affected families for study. With the use of X-chromosomal probes, restriction fragment length polymorphism, and linkage statistical analysis, the hypophosphatemic gene has now been localized to the Xp22 chromosomal band,⁴³⁻⁴⁵ in close proximity to the recently identified Duchenne/Becker muscular dystrophy gene.

Recently, a second murine hypophosphatemic gene closely linked to the Hyp gene, the Gy gene (named for the Gyro mouse), has been reported⁵² with cochlear and vestibular defects. The discovery of the Gy gene will help in the further identification of the gene defect in the human disorder.⁵² The presence of two related defects in the

mouse—the hypophosphatemia and the cochlear-vestibular abnormalities associated with hypophosphatemia—raises the possibility of two linked disease loci in humans. It is hoped that work in progress with newer markers, subtraction hybridization, automated DNA sequencing, and the polymerase chain reaction technique will “close in” on the hypophosphatemic gene in humans in the near future.

QUESTIONS FOR THE FUTURE

Many questions remain unanswered. The use of magnetic resonance spectroscopy⁴³ will examine intracellular phosphate and energy metabolism in various test conditions; isolation and characterization of the humoral factor⁴⁶ will substantially advance our understanding of phosphate metabolism. Linkage studies^{47-51,53} to characterize the two phenotypes⁵² will assist in the isolation of the gene and eventually lead to the delineation of its protein expression product for early diagnosis. With the rapid advances in molecular biology, it is conceivable that gene therapy will be available in the next generation for affected individuals. This is one example of how basic research can lead to definitive treatment.

We thank Marilyn Reilly for secretarial assistance and Martha D. Massie, RD, and Martha D. Wellons for editorial assistance.

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Studies in Fetal Malnutrition

Warren M. Crosby, MD

● Fetal malnutrition, a worldwide problem, is accompanied by varying degrees of lifelong morbidity for the child. Only 25% of fetal malnutrition is accomplished by maternal risk factors known to cause intrauterine growth retardation (ie, chronic hypertension, advanced diabetes mellitus, or severe preeclampsia). If the malnourished fetus could be detected early in pregnancy, nutritional intervention might be successful in improving fetal growth rate and in avoiding the morbidity due to malnutrition. This communication reviews the almost 40 years of studies by Jack Metcalf, MD, and coworkers to unravel the causes of fetal malnutrition and their efforts to prevent it.

(AJDC. 1991;145:871-876)

Fetal malnutrition, a term coined by Usher, can be found in every country and culture and at every socioeconomic level.¹ The effect of nutritional deprivation in utero is to decrease the child's potential for a normal productive life after birth. Specifically, increased perinatal morbidity,² poor postnatal growth,³ reduced numbers of brain cells,⁴ altered myelin,⁵ neurologic difficulties,⁶ and impaired learning ability^{7,8} have each been shown to be associated with fetal malnutrition. Fetal malnutrition can be

nutrition that occurs in an apparently uncomplicated pregnancy in an apparently healthy mother with a diet consistent with her peers whose babies are not malnourished cries out for an explanation and prevention.

During World War II, Jack Metcalf, MD, was trained in nutrition at the Harvard School of Public Health, Boston, Mass. Following completion of this training he was assigned to the United Nations Relief and Rehabilitation Administration as a public health service officer. He spent a year in Italy surveying the nutritional status of high-risk groups in anticipation of the initiation of the Marshall Plan. After this assignment he returned to Boston. Both in Italy and in Mexico City's Hospital Infantil, Metcalf studied children with severe malnutrition and found that simply refeeding and rehydrating severely malnourished children did not always prevent their death. Indeed, one of the early publications¹¹ reported that eight of 13 children hospitalized with severe protein energy malnutrition in the study died of their disease. One of the first to study intracellular changes in this condition, Metcalf found in the muscle cells of these starved children differences from those obtained from normal children. It had been shown previously by Metcalf and others¹¹ that muscle cells obtained by small percutaneous needle biopsies from children with kwashiorkor contained more water and sodium content with depleted concentrations of sodium, potassium, and magnesium. Because these differences widen just prior to death, it was believed that rapid decline in intracellular energy production would account for the findings. Investigation of intracellular energy production offered promise of finding a way to prevent death if the intracellular processes could be reversed. The first report using newer microanalytic methods that allowed simultaneous analysis of more components of cellular energy metabolism was published in *Medicine* in 1966,¹¹ and reported successful measurement of pyruvate kinase, lactate, malic, and isocitric dehydrogenase enzymes and concentrations of sodium, potassium, chloride, phosphoenol pyruvate, pyruvate, alpha-ketoglutarate, and oxaloacetate. As expected, muscle cells from these 13 starving children contained increased water and sodium, with significant reduction in the concentration of potassium, phosphoenol pyruvate, and oxaloacetate. The activities of each of these intracellular enzymes, except lactate dehydrogenase, were substantially lower in the starving children as compared with normal controls. Kinetic studies of pyruvate kinase were carried out in three children, all of whom showed that the enzyme was both quantitatively and qualitatively deficient in starving children.

See also pp 853, 860, 865, and 877.

identified in 2% to 3% of newborns in the United States and has been estimated to be as frequent as 8% to 10% in developing countries.⁹ Fetal malnutrition is not simply dependent on maternal malnutrition, although the latter plays a role. Other maternal diseases besides malnutrition are known to be associated with undergrown newborns. That maternal hypertension, chronic and the acute form of preeclampsia-eclampsia, and advanced diabetes mellitus regularly produce small-for-date babies, implies that the vascular component of these diseases can reduce uteroplacental blood flow sufficiently to restrict the normal flow of nutrients to the fetus. However, only about 25% to 30% of undergrown newborns occur in mothers with such diseases.¹⁰ It is clear that fetal malnutrition is a complex disease, and one with many causes. Fetal mal-

Accepted for publication December 26, 1990.

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Reprints not available.

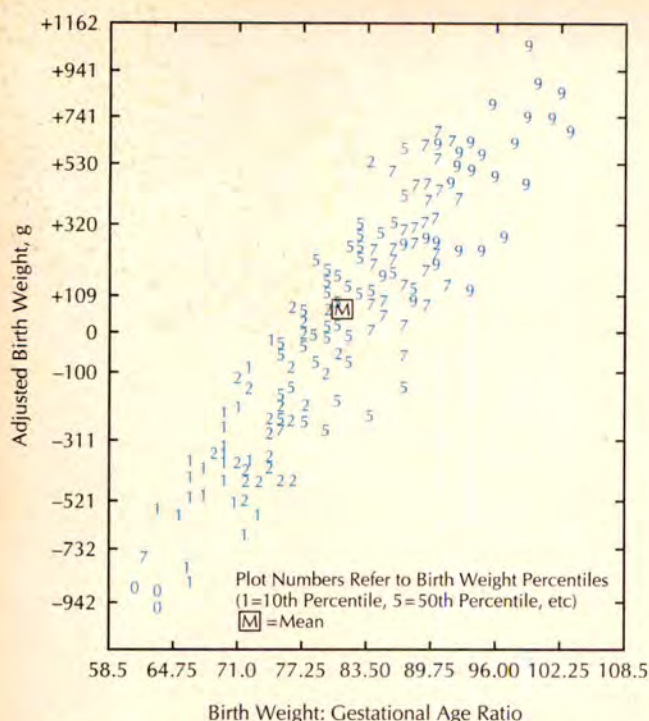


Fig 1.—The relationship between the adjusted birth weight, birth weight-gestational age ratio, and actual birth weight percentiles (Lubchenko²). The clear linearity shows an excellent correlation between all three criteria for appropriate size at birth and confirms the concept that fetal growth is a continuum with malnourished babies on one end and overgrown babies at the other.

Performing muscle biopsies or liver biopsies on dying children is an onerous task and also may have been harmful. The next year, Metcalf et al¹² reported that leukocytes obtained by simple venipuncture in starving children had alterations in energy metabolism similar to muscle cells obtained by biopsy. While muscle cells account for the largest part of the body's production and consumption of energy, it appeared that leukocytes could serve as biochemical surrogates for muscle cells in studies of protein energy malnutrition.¹³ Leukocytes from 16 severely and four moderately malnourished children were studied and compared with leukocytes from normal controls. Substantial decreases in the cellular content of oxaloacetate, pyruvate, and lactate were found. However, in the moderately malnourished children, only minor changes were seen, suggesting that alterations in cellular energy metabolism can be detected only in leukocytes from severely malnourished children. Adenosine diphosphate levels in the leukocytes from the most severely malnourished children were markedly decreased, while the decrease in adenosine triphosphate and adenosine monophosphate concentrations was not significant. It was believed that the data indicated that severe protein energy malnutrition produces significant alteration in cellular energy production characterized by inhibition of the terminal step in glycolysis: the production of adenosine triphosphate by the enzyme pyruvate kinase.¹³

Krebs and Eggleston¹⁴ had shown that starvation decreases the activity of pyruvate kinase in the liver and refeeding with carbohydrates induces biosynthesis of the enzyme. Severely malnourished children composed a substantial part of infant mortality in Mexico City. It became

Table 1.—Differences Between Smokers and Nonsmokers

Variable	No.	Mean smokers	No.	Mean nonsmoker	P
Adjusted birth weight	59	-94	99	+56	<.05
Adjusted baby length	59	-0.57	99	+0.34	<.05
Maternal height	77	163	129	160	<.01
Pyruvate kinase	47	11,197	70	12,414	<.05
RNA synthesis	43	18	67	23	<.01
Total carotene	42	96	67	115	<.01
Amino acids					
Aspartic acid*†	13	42	39	57	<.01
Threonine*‡	13	166	39	211	<.001
Serine*	13	139	39	173	<.01
Proline	12	176	39	247	<.01
Alanine	12	310	39	388	<.01
Valine‡	12	149	39	190	<.001
Isoleucine‡	13	60	38	77	<.001
Leucine*‡	13	105	38	138	<.001
Tyrosine*‡	13	58	38	69	<.01
Phenylalanine*†‡	13	64	38	80	<.001
Lysine*†‡	13	143	38	191	<.001
Histidine*†‡	13	90	39	102	<.05
Arginine*†	13	132	39	164	<.01
Ornithine*	12	34	39	43	<.001

*Correlated with adjusted birth weight (entire group).

†Correlated with adjusted birth weight of nonsmokers.

‡Essential amino acid.

apparent that small-for-date babies born in that city frequently displayed many of the clinical and biochemical characteristics of malnutrition previously identified in starving children. In addition, analysis of leukocytes from these newborns showed intracellular changes in energy metabolism that were comparable to those changes seen in older children with malnutrition. Studies of leukocytes from the fetus obtained from cord blood samples at birth and compared with studies of the mother's leukocytes drawn at the same time showed changes in energy metabolism of the leukocytes in the mother that were similar to those found in the malnourished fetus. Comparing mothers' leukocyte energy metabolism with the leukocyte energy metabolism of their neighbors who had recently given birth to normal-sized children showed that the mothers of malnourished newborns were different from the mothers of normal children despite the fact that the mothers generally lived in the same area and ate similar diets. Thus, in an overview of malnutrition published in the *Annual Review of Medicine*, Metcalf⁹ stated "in all probability the maternal environment is more important to fetal growth than genetic factors." These findings—altered cellular energy metabolism in children with severe protein energy malnutrition; that these alterations were found in leukocytes and muscle and liver cells obtained from these children; and similar alteration of energy metabolism in leukocytes from small-for-date newborns and their mothers—raised the possibility that analysis of maternal leukocyte energy metabolism might permit antepartum diagnosis of fetal malnutrition.

This concept was pursued in Mexico City, where a study was carried out to see if it were possible to identify those

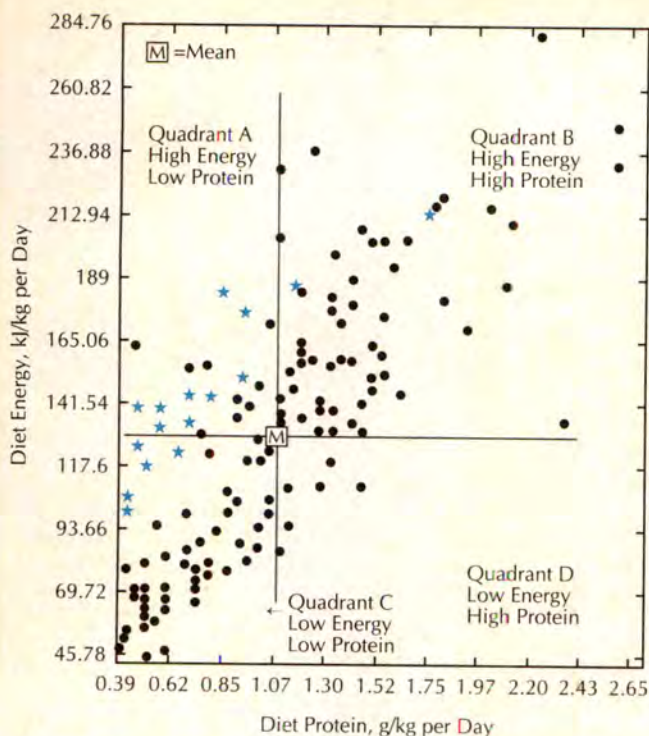


Fig 2.—The relationship between maternal intake of protein and energy at midpregnancy and the adjusted birth weight. The general linear relationship shows a strong correlation between maternal intake and adjusted birth weight. Dot indicates mothers whose adjusted birth weights were normal; star, those mothers whose babies had adjusted birth weights that were below 1 SD. Nine of the 15 undergrown babies were in the low energy-low protein quadrant.¹⁵

mothers who were to have malnourished fetuses and identify them early in pregnancy so that a nutritional intervention might prevent the fetal malnutrition.¹² This study suggested that the normal metabolic activity of leukocytes is altered somewhat in late pregnancy, prior to labor, in mothers carrying malnourished fetuses.¹² Similar alteration was reported for leukocyte RNA synthesis. It was suggested that whatever factor[s] was responsible for this alteration of maternal leukocytes also altered the energy metabolism of fetal cells. Thus, this pilot study confirmed that study of the mother's leukocytes in midpregnancy identified fetuses with a high likelihood of protein energy malnutrition; with in utero diagnosis, it should be possible to provide nutritional intervention for the mother in an attempt to decrease malnutrition in her fetus.

This concept was pursued by a controlled prospective study of the relationship between a large number of maternal factors and fetal malnutrition. This study also introduced the concept of "adjusted birth weight" to allow for more definitive identification of the malnourished fetus. This concept depends on adjusting the actual birth weight of the fetus to those demographic factors of the parents that are known to affect birth weight.

Reported were the cases of 182 patients from the University of Oklahoma (Oklahoma City) prenatal clinics whose length of gestation clinically matched their ultrasound measurements, and who had otherwise normal pregnancies that resulted in deliveries between 35 and 43 weeks of gestation.¹⁵ The length of pregnancy was corroborated by a Dubowitz score following birth. To account for the genetic variability in birth weight adjustments for

Table 2.—Multiple Regression (Dependent Variable: Adjusted Birth Weight)*

Independent Variable

Total carotenes
Family income
Maternal weight at 24 wk
Leukocyte adenosine diphosphate
α_1 globulin
Leukocyte phosphofructokinase
Cigarette smoking (—)
Leukocyte protein: DNA ratio (cell size)
Leukocyte RNA synthesis

* $R = .4982$; $P < .05$. Thirty independent variables were analyzed (amino acid concentration not included). All Correlations were positive except maternal smoking.

maternal age, race, parity, height, prepregnancy weight, and weight gain during pregnancy as well as the week of gestation of birth and the sex of the babies were combined to produce an adjusted birth weight that was calculated for each newborn. Each adjustment was made according to previously reported influences of these factors on birth size adjusted by multiple regression analysis of those factors in the study mothers. The adjusted birth weight, thus, was what a given sex baby in a given mother at a particular week of gestation *should* weigh. This was compared with what the newborn actually did weigh and its actual sex and birth week.

The formula used for calculation of adjusted birth weight is as follows:

$$\begin{aligned} \text{Adjusted Birth Weight} = & 1491.9 + 126.1 \times \\ & \text{Gestational Age in Weeks} - 101.5 \times \\ & \text{Sex (Males} = 1, \text{ Females} = 0) - 150.3 \times \\ & \text{Week of Gestation at Entry} - 130.3 \times \\ & \text{Race (White} = 0, \text{ Nonwhite} = 1) + \\ & 72.0 \times \text{Height (cm)} + 98.0 \times \\ & \text{Weight at Entry (kg)} + 87.1 \times \\ & \text{Nonpregnant Weight (kg)} - 108.3 \times \\ & \text{Smoking (No Smoking} = \\ & 0, \text{ Up to 10 Cigarettes/d} = \\ & 1, \text{ 11 to 20 Cigarettes/d} = \\ & 2, \text{ 21 to 30 Cigarettes/d} = 3, \\ & \text{and } \geq 31 \text{ Cigarettes/d} = 4) + 119.5 \times \\ & \text{Fundal Height at Entry (cm)} + 43.5 \times \\ & \text{Parity Including This Pregnancy (No.)} \end{aligned}$$

The differences between the adjusted birth weight and the actual one thus reflected the degree of overgrowth or undergrowth of the baby. It became clear that there is a continuum of appropriate fetal growth from very small to very large. For statistical purposes, the study defined a fetus whose adjusted birth weight was 1 SD below the mean as having fetal malnutrition, while those that weighed more than 1 SD above the mean were termed "macrosomic." A small-for-gestational-age baby, one that was termed as having fetal malnutrition, could thus be defined with more precision than previously. Figure 1 shows there is a linear relationship between three different criteria of appropriate fetal size at birth.

This study¹⁵ introduced the important concept of the adjusted birth weight and showed that it correlated with biochemical factors measured in maternal leukocytes.

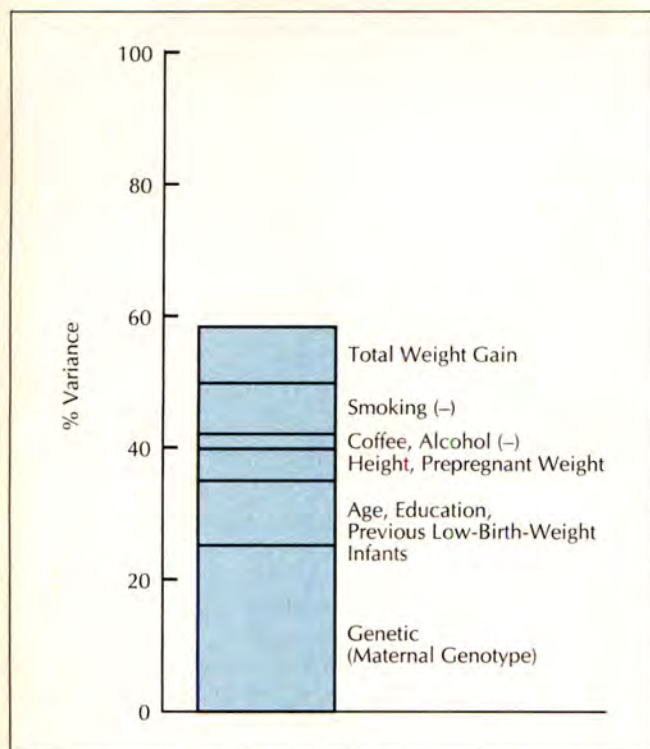


Fig 3.—Percent variance in birth weight due to various characteristics by multiple regression analysis

From this study, the largest contributor to fetal size at birth was length of gestation. Smoking had a clear negative effect on adjusted birth weight. So much so in fact, that to study the relationship of the many factors measured in the plasma and leukocytes and comparing them with adjusted birth weight, the initial study group was divided into smokers and nonsmokers. The relationship between the two is shown in Table 1.

The plasma constituent measured at midpregnancy that most highly correlated with fetal malnutrition was carotene. This finding was entirely unexpected. The maternal serum carotene level was negatively correlated with maternal smoking, but the correlation with fetal malnutrition was even greater in nonsmoking mothers. Similarly, plasma zinc level was also correlated directly with adjusted birth weight. Maternal serum concentration of amino acids, like carotene and zinc, was found to correlate with fetal growth. Ten amino acid levels in maternal serum had a statistically significant correlation with adjusted birth weight.¹⁵

The data in this study were analyzed by linear and by multiple regression techniques. Linear regression identified the rank order of factors that make up the contributions to adjusted birth weight. Figure 2 shows the relationship between maternal protein and energy intake and the adjusted birth weight of the baby.

Multiple regression analysis identified the effect of several variables on a single variable. In this analysis, nine variables contributed at the .05 level to adjusted birth weight. Table 2 shows this relationship. Beta-carotene and smoking headed the list, followed by family income. While some of these correlations had been observed by others, the mechanism by which an individual factor influences fetal growth is entirely unknown.

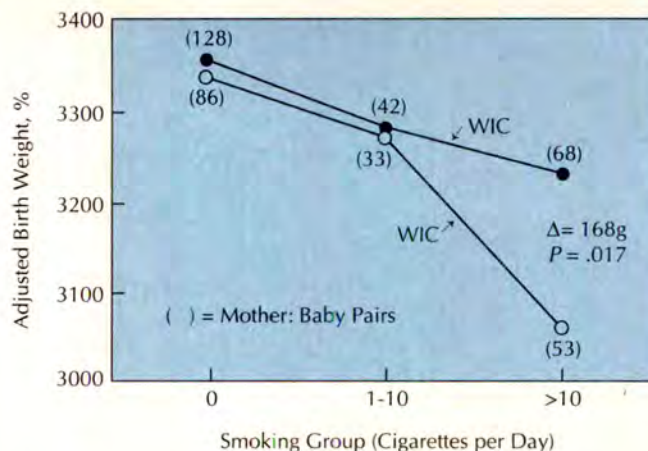


Fig 4.—Interaction of special supplemental food program for women, infants, and children (WIC) and smoking on birth weight. This was adjusted for gestational age, sex, prenatal visits, race, interval since last pregnancy, previous low-birth-weight babies, and entry weight. The graph shows the overall effects of WIC and smoking.

The leukocyte data also showed correlation of energy metabolism of the leukocyte with adjusted birth weight. The adenosine diphosphate generation, phosphofructokinase activity, RNA synthesis, and cell size each correlated with adjusted birth weight at a .05 level of significance.¹⁵

It is clear from this study that many things that control leukocyte metabolism also relate to the growth of the fetus. This study identified those factors that can be measured in maternal blood in midpregnancy that correlate significantly with the presence of a malnourished fetus at birth.

Further studies by McClain et al¹⁶ continued to demonstrate positive correlations between serum amino acid levels in midpregnancy and the baby's size at birth. They showed that the concentration of total free amino acids in plasma from mothers carrying malnourished fetuses was significantly lower than from mothers having normal-sized fetuses at birth. Abnormally low levels of aspartic acid, serine, alanine, tyrosine, ornithine, and arginine correlated with fetal malnutrition. The branched chain amino acids, isoleucine and valine, were at normal levels in mothers with malnourished fetuses.¹⁶

From the enormous complexity indicated by the relationship of this multitude of serum and intracellular metabolic components with fetal growth, the concept of nutritional interrelationships interfering with normal fetal growth began to emerge. In a lecture to the symposium on The Year of the Child in Ontario, Canada, in 1979, Metcalf¹⁷ reported that the various maternal supplemental feeding experiments that had been performed in developing countries had a small influence on average birth weight. An increase of 60 to 80 g was seen to be hardly worth the effort. But Metcalf pointed out in these studies that every mother in the experimental group was given supplemental nourishment. Because most of the fetuses in that group of women were not malnourished in the first place, the supplement would be expected to have little effect on them. The weight gain for malnourished fetuses produced by maternal feeding is thus diluted by the weight of the normal fetuses for which maternal feeding was not necessary. Mothers of most malnourished fetuses are not malnourished themselves; supplementation of diet

in an across-the-board study might be predicted to have little detectable effect on the mean birth weight for the entire group. Nutritional imbalances are probably as important as a simple deficiency, and simple deficiencies in maternal diets, except in rare instances, are not found in developed countries.

The concept that complex interrelationships between various nutrients that affect fetal growth was tested in a study using inbred rats in 1981.¹⁸ In this study, three groups of pregnant rats were fed similar diets containing narrowly similar amounts of protein and energy. The two experimental groups were provided diets containing excess disposable amino acids with adequate net protein and energy intakes. One of the two experimental groups differed by having threonine limited from the otherwise normal protein and energy diet. Fetal growth retardation occurred in both of the experimental groups and was greatest in the threonine-restricted group. The conclusion of the study was that a relative excess of small neutral amino acids which, along with the larger neutral amino acids, competes with threonine for transport into cells. When there is adequate threonine concentration in the serum, the excess of small neutral amino acids limits entry of threonine into cells. By further limiting intake of threonine, an essential amino acid, the effect is augmented and fetal growth retardation becomes worse. Furthermore, this study was designed to test the concept that maternal catabolism would be able to correct the imbalance by the provision of the diminished amino acid supplies from the mother's protein stores. This did not occur and, at least in this instance, it appears that maternal protein catabolism cannot make up the difference when imbalance rather than a deficiency occurs in her diet.

In a later article, Metcalf et al¹⁹ state "maternal genetic factors account for about 25% of variance in birth weight" and "the fathers genetic contribution to the variance is only about 1 to 2%." As shown in Fig 3, the proportions of variance in birth weight accounted for by some maternal characteristics and environmental factors are as follows: maternal age, education, and previous delivery of low-birth-weight infant account for 8% of the variance; maternal height and prepregnant weight explain another 8%. Coffee and alcohol consumption have a negative influence on fetal growth and contribute about 2% of the variance. Cigarette smoking has a major deleterious influence and accounts for 3% to 6% of the variation and the effect is related to the number of cigarettes smoked per day.

Maternal weight gain from midpregnancy to term contributes about 3% of the variance, and total weight gain during pregnancy contributes another 3% to 6%. Metcalf goes on to say that this report shows that birth weight is related to maternal nutrition and can be predicted from a set of maternal characteristics and nutrition-related measurements obtained in midpregnancy.

During the 1970s and early 1980s, the registration of patients from the prenatal clinics at the University of Oklahoma Hospitals continued. The next study of these women was supported by the US Department of Agriculture and was based on the food supplementation program of that department (Special Supplemental Food Program for Women, Infants and Children [WIC]) and was designed to test the hypotheses that women destined to have malnourished newborns could be identified at midpregnancy with the prediction equation based on previous subjects drawn from the same population using both de-

mographic and biochemical data.²⁰ This study enrolled patients based on predicted fetal malnutrition. (The prediction was based on those maternal demographic factors that had been correlated with fetal malnutrition in previous studies.) The demographic equation identified 226 women who were predicted to have either large or small babies of the 410 enrolled in the study. One third of all of the mothers' diets were unsupplemented and two thirds of the mothers were given standard WIC supplementations. The results of this study indicated that, aside from the week of gestation during which birth occurred, the strongest maternal effect on adjusted birth weight was smoking. Of interest, however, is that WIC supplementation ameliorated the negative effect of smoking on birth weight (Fig 4). The effect was dose dependent, ie, the greatest effect of smoking on unsupplemented mothers increased with the number of cigarettes smoked per day, but the difference could be seen only at a daily smoking level of more than 10 cigarettes per day.

Because of previous findings that carotene and, to a lesser extent, cholesterol, correlated with fetal malnutrition, the next study, again supported by the US Department of Agriculture, reported the relationships between midpregnancy maternal plasma levels of carotene and cholesterol in relationship to birth weight in smoking and nonsmoking mothers.²¹ The outcome of these studies is curious, but it reflects the complex interaction of levels of plasma nutrients and fetal malnutrition. The heavy hand of cigarette smoking can also be seen. This study indicated that smoking not only reduced the birth weight of malnourished fetuses, but it also altered the relationship between carotene, cholesterol, and birth weight. Smoking continued to show a negative effect on fetal growth, and in nonsmokers there was a clear relationship between plasma cholesterol level and adjusted birth weight. The interactive effect of smoking, cholesterol, and carotene on birth weight was significant ($P = .017$) after adjusting for the demographic factors and gestational age.

From these studies and from the observations of others, our understanding of the relationship between maternal nutrition and fetal growth and development leaves a lot to be desired. The growth and reproductive functions of the billions of cells in the body and the biochemical interactions across cellular membranes are poorly understood because of the enormous complexity between the various molecules that are transported across cell membranes and what happens to them in the process of metabolism. This complexity is made considerably more difficult when one tries to study the process in the developing fetus because of the interposition of both maternal nutrition, the placenta, and changes in cellular metabolism of the fetus as it matures.

The contributions of Jack Metcalf to the understanding of the relationship between maternal nutrition and fetal growth and development during a 40-year period has enabled us to recognize the complexity and to identify those relationships that can be measured so that the likelihood for fetal malnutrition can be quantified by studying the mother in midpregnancy. Since we still do not understand the relationship between maternal nutrition and fetal development directly, nutritional intervention is still confined to "shotgun" approaches.

From this professional lifetime of study, several salient points are evident: (1) Fetal malnutrition resembles postnatal malnutrition and appears to have many of the same

cellular changes. (2) Fetal malnutrition is a complex disorder and has many causes, including genetic, placental insufficiency caused by maternal vascular and other diseases, and, as Metcalf's studies have shown, by derangements and imbalances of various nutrients in the maternal biochemical milieu that are apparently entirely apart from known maternal diseases. (3) The concept of adjusted birth weight is an important tool to increase the precision by which we can identify malnutrition in the newborn.

The clinical observation of subjective factors such as wrinkled skin and apparent deficiency of subcutaneous fat is entirely too crude a variable on which to compare the outcome of nutritional interference. Similarly, actual birth weight is so much dependent on racial and demographic factors that raw birth weight itself is also too crude a measurement for appropriate use. Metcalf has shown that fetal nutrition, like normal growth and development, is a continuum from inadequate to excessive and that the inadequacies and excesses are not just simply related to the dietary intake of the mother. By using the adjusted birth weight, a calculation based on demographic factors that indicates what a given fetus in a given mother should weigh at a given week of gestation, the researcher acquires the opportunity to be more precise in studying the relationship of maternal nutrition to fetal growth.

The use of the leukocyte as a surrogate for the rapidly growing and developing cells of the fetus was also a major contribution to our ability to study fetal malnutrition. Metcalf's illustration of the relationships between maternal leukocyte biochemistry and fetal growth is important. However, there are differences between leukocytes and developing cells and perhaps these differences limited our capability for drawing direct inferences from the findings of leukocyte metabolism and that of the cells of the growing fetus.

Of most importance, perhaps, is Metcalf's demonstration of the enormous complexity of the system. His rat study pointed out that even with excess availability of amino acids in the maternal serum, fetal malnutrition still could occur when combinations of these amino acids interfered with the transfer mechanisms of other amino acids across cell membranes. Our understanding of individual mechanisms that only alter cellular metabolism, but do not kill the cell, is sparse. In most cases we do not know precisely what the effect of halving or doubling of the concentration of a molecule such as carotene will do to cellular growth and development, whether we are measuring that concentration in the maternal serum, the fetal serum, the fetal interstitial space, or within the fetal cells themselves. If we are ever to develop the capability of reversing fetal malnutrition prior to birth, we will need to better understand these complex interrelationships. Jack Metcalf has laid some of the groundwork for this process. By the use of Metcalf's concepts, we should be able to identify those fetuses at greatest risk for malnutrition and apply an appropriate nutritional intervention. Sooner or later this will become possible with precision. Those malnourished fetuses should, with prenatal treatment, be able to start independent life with a healthier set of organs and a better capability to become contributing rather than dependent citizens.

The following persons have played major roles in the series of studies of fetal malnutrition performed in Dr Metcalf's laboratories: Paul

Costiloe, PhD; Harold Sandstead, MD; C. E. Bodwell, PhD; Joan Wikman-Coffelt, PhD; Alfonso Bernal, MD; Pablo Yoshida, MD; Silvestre Frank, MD; Luis Velasco, MD; A. Sosa; Gail Jacobson; Carolyn Johnson; Larry Bentle, PhD; Timothy Cole; Carmen de la Pena; Elizabeth Kaiser, PhD; Dutta Seshachalam, PhD; David Milne, PhD; Stephen Majors; Takashi Yoshida, MD; Adolfo Rosado, MD, PhD; Juan Urrusti, MD; Ricardo Madrazo, MD; Myriam Morales, MS; M. Mameesh; Philip McClain, PhD; James Gable; Frances Weaver, RD; Richard Luff; Ramon Torres Pinedo, MD; John Hansen, MD.

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Partial Hypoparathyroidism

A Variant of Transient Congenital Hypoparathyroidism

Sang Whay Kooh, MD, FRCPC, Ann Binet, BSc, RN

• We encountered three children who had neonatal hypocalcemia followed by a period of normocalcemia and recurrence of hypocalcemia later in childhood. They were full-term infants with normal birth weights who developed hypocalcemia within the first 48 hours after birth. The hypocalcemia resolved in 1 week, 3 months, and 14 months in the three patients. The recurrences of hypocalcemia occurred at 4, 7, and 12 years of age. Their plasma parathyroid hormone concentrations were consistently low but detectable. We suggest that partial hypoparathyroidism is the underlying abnormality in these patients and that neonatal hypocalcemia in otherwise healthy infants indicates the need for calcium measurements during childhood and adolescence.

(AJDC. 1991;145:877-880)

Most cases of hypocalcemia during the neonatal period are transient.¹ It seldom signals the onset of a permanent disorder of calcium homeostasis, such as primary hypoparathyroidism. However, some children who develop symptomatic hypocalcemia during the neonatal period that requires treatment for weeks to months ultimately recover from hypocalcemia. The diagnosis of transient congenital hypoparathyroidism has been applied to this condition.^{2,3} Bainbridge et al⁴ questioned

a Nova Stat Profile 4 (Nova Biochemical, Waltham, Mass). The reference ranges and conversion factors from millimoles per liter to milligrams per deciliter are shown in the Table. Plasma parathyroid hormone (PTH) was assayed until 1986 by radioimmunoassay with antisera directed toward the N- and C-terminals of the PTH molecule and from 1987 to the present by an immunoradiometric method with the intact PTH kit (ALLEGRO, Nichols Institute, Los Angeles, Calif). The normal reference range for the intact PTH assay was 10 to 65 ng/L, and the sensitivity of the assay was 1 ng/L. The reference range for the assays performed before 1987 was adjusted so that these values also ranged from 10 to 65 ng/L.

PATIENTS

PATIENT 1.—Patient 1 was born June 29, 1974. The biochemical findings and treatment of this female patient are presented in Fig 1. The patient was born at a local hospital at 38 weeks' gestation with a birth weight of 2930 g. She became irritable and developed tonic-clonic convulsions on the first day of life. Plasma chemistry levels were as follows: calcium, 1.43 mmol/L; magnesium, 0.86 mmol/L; and phosphate 1.95 mmol/L. Intravenous and oral calcium treatment improved the hypocalcemia, and the patient was sent home without medication at 1 week of age. The plasma calcium level at the time of discharge was 2.15 mmol/L. The plasma calcium and phosphate levels were normal in both parents. She was hospitalized again at 4 weeks of age for investigation of asymptomatic hypocalcemia and was subsequently transferred

See also pp 853, 860, 865, and 871.

whether these patients truly recover from hypoparathyroidism and speculated that the patients who recover from the neonatal hypocalcemia have a compensated form of hypoparathyroidism. Herein, we describe three patients who had neonatal hypocalcemia followed by a period of normocalcemia and then a recurrence of hypocalcemia later during childhood.

METHODS

Plasma calcium, magnesium, and phosphate levels were measured with a Kodak Ektachem 400 analyzer (Eastman Kodak Co, Rochester, NY) from 1984 to 1988 and a Kodak Ektachem 700 analyzer since 1989. The ionized calcium level was analyzed with

Accepted for publication April 21, 1991.

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Reference Ranges and Conversion Factors for Calcium, Magnesium, and Phosphate Level

Variable	Reference Value mmol/L	Conversion Factor	Value, mg/dL
Calcium	2.25-2.59	4.0	9.00-10.36
Magnesium			
Newborn	0.75-1.15	2.4	1.80-2.67
Children	0.70-0.94		1.68-2.28
Adults	0.65-1.00		1.56-2.40
Phosphate			
Birth-1 mo	1.62-3.10	3.1	5.02-9.61
1-4 mo	1.55-2.62		4.81-8.12
4 mo-1 y	1.30-2.20		4.03-6.82
1-4 y	1.16-2.10		3.60-6.51
4-8 y	1.16-1.81		3.60-5.61
9-14 y	1.07-1.71		3.32-5.30
15 y+	0.87-1.52		2.70-4.71

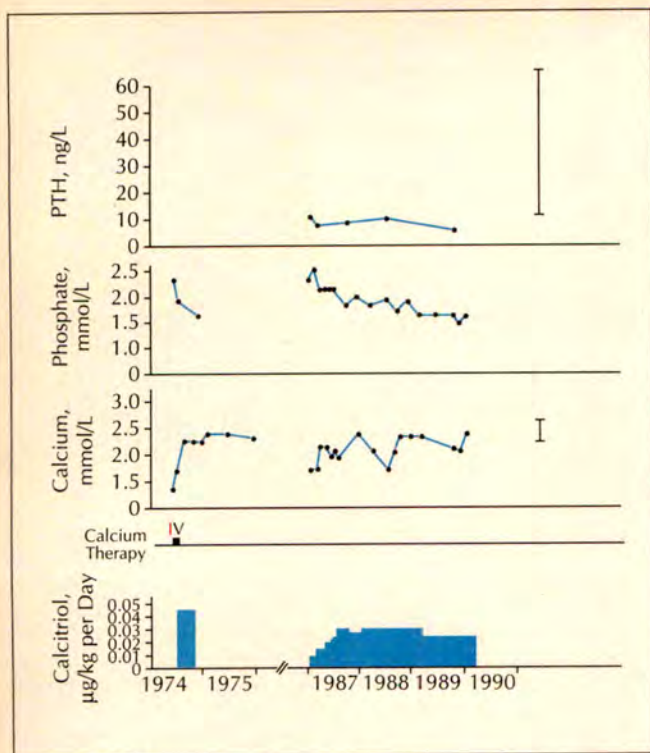


Fig 1.—Case 1. Plasma parathyroid hormone (PTH), phosphate, and calcium concentrations and treatment. Vertical bars indicate normal reference range; IV, intravenous.

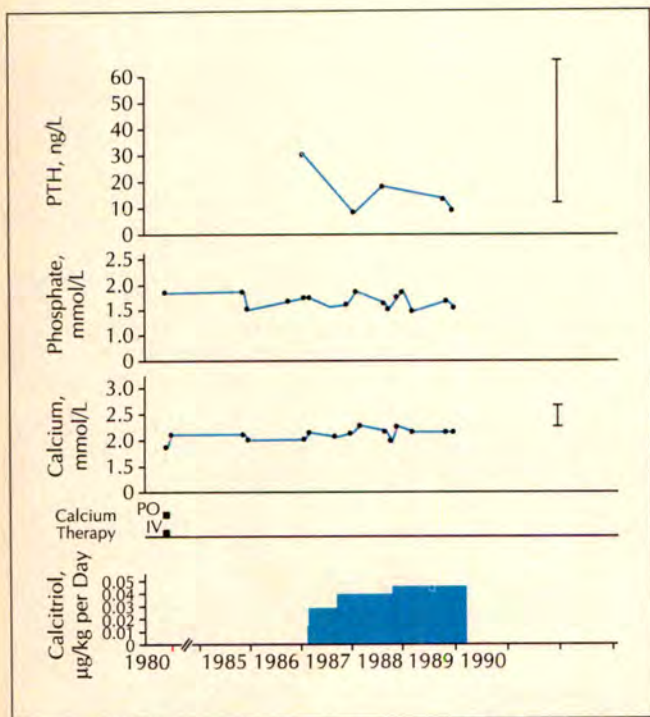


Fig 2.—Case 2. Plasma parathyroid hormone (PTH), phosphate, and calcium concentrations and treatment. Vertical bars indicate normal reference range; PO, by mouth; and IV, intravenous.

to our hospital on July 31, 1974. The plasma calcium level was 1.70 mmol/L, and the phosphate level was 2.80 mmol/L. She was treated with intravenous calcium and oral calcitriol (1,25-dihydroxyvitamin D₃), which was later changed to 1 α -hydroxyvitamin D₃. Results of immunologic studies were normal. She was discharged from the hospital at 3 months of age

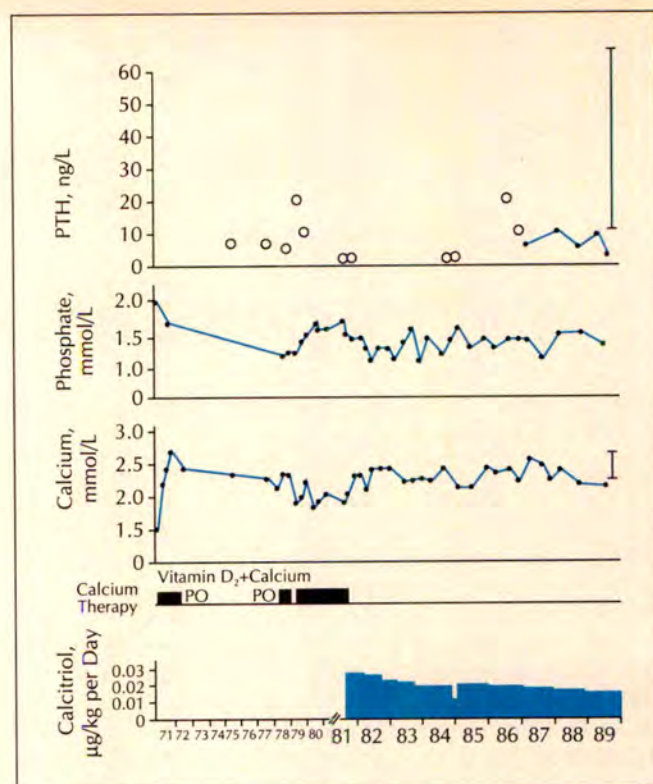


Fig 3.—Case 3. Plasma parathyroid hormone (PTH), phosphate, and calcium concentrations and treatment. Open circles indicate PTH values before 1987, adjusted to represent their relative value equivalent to those determined by the present immunoradiometric assay (see "Methods" section); closed circles, PTH values determined with presently used radiometric method (see "Methods" section); and vertical bars, normal reference range; PO, by mouth; and IV, intravenous.

when the plasma calcium levels could be maintained above 2.00 mmol/L. Shortly thereafter, 1 α -hydroxyvitamin D₃ therapy was discontinued, with frequent monitoring of plasma calcium levels; plasma calcium levels were maintained above 2.25 mmol/L. At 18 months of age, the calcium level was 2.45 mmol/L and the phosphate level was 1.77 mmol/L.

Except for a generalized developmental delay, first noted at 7 months of age, the patient had no clinically important illnesses until she was 12 1/2 years of age in 1986, at which time she began to experience difficulty bending her fingers and numbness of her hands and feet. Several months later, following a minor viral illness, she lost consciousness while watching television. On admission to a local hospital, she had a plasma calcium concentration of 1.35 mmol/L, an ionized calcium level of 0.69 mmol/L (reference range, 1.10 to 1.30 mmol/L), a phosphate level of 2.45 mmol/L, and a PTH level of 28 pmol/L (reference range, 29 to 85 pmol/L). The electroencephalogram was interpreted as showing "abnormalities consistent with a metabolic disorder."

During the last 3 years, she has received therapy with calcitriol, ranging from 0.02 to 0.03 μ g/kg per day, and has maintained a plasma calcium concentration between 2.05 and 2.35 mmol/L, a phosphate level between 1.40 and 1.65 mmol/L, and a PTH level of 5 to 9 ng/L. She has had frequent minor viral illnesses but no bacterial infections. She attends a special class for the learning impaired. The renal responses to exogenous PTH were tested in 1990. Injection of human PTH (1-38, Bissendorf Peptide GmbH, Wedemark, Germany) raised the cyclic adenosine monophosphate excretion rates 55-fold and decreased the tubular reabsorption of phosphate from 93% to 67%.

PATIENT 2.—Patient 2 was born November 20, 1980. The biochemical findings and treatment of this female patient are shown in Fig 2. She was born after a normal pregnancy at a birth weight

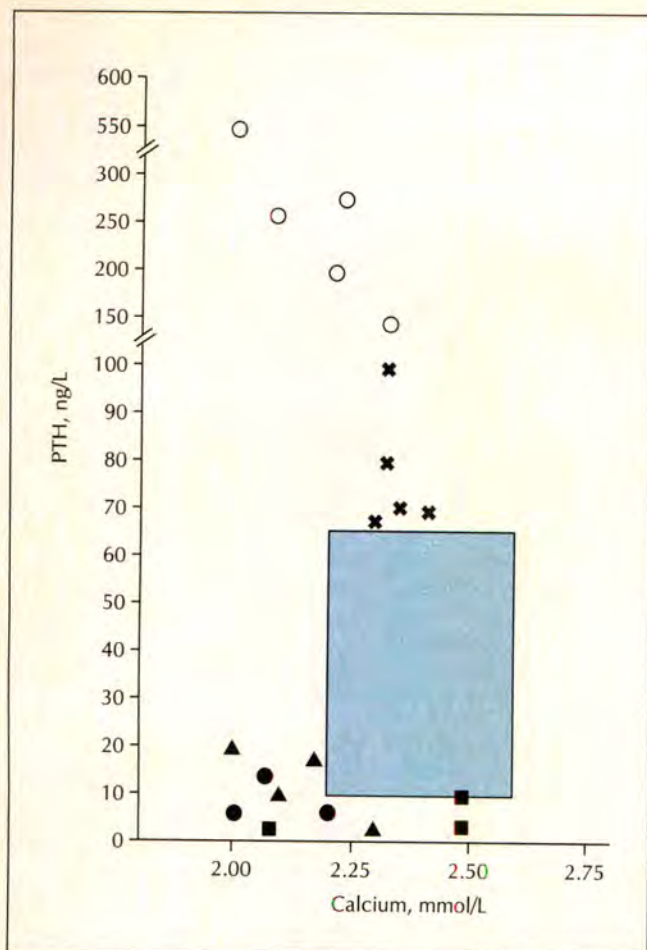


Fig 4.—Plasma calcium and parathyroid hormone (PTH) concentrations of various parathyroid disorders. Solid circles indicate partial hypoparathyroidism; open circles, pseudohypoparathyroidism type I (A and B); X's, secondary hyperparathyroidism (X-linked hypophosphatemia treated with phosphate); solid squares, MEDAC (multiple endocrine deficiency, Addison's disease, and candidiasis); triangles, DiGeorge syndrome; and large shaded square area, normal calcium and PTH values.

of 2860 g. On the second day of life, she was noted to be "dusky" around the mouth. A chest roentgenogram and an electrocardiogram were normal. The plasma calcium concentration was found to be 1.55 mmol/L, the magnesium level was 0.75 mmol/L, and the phosphate level was 2.42 mmol/L. The maternal plasma calcium, phosphate, and PTH concentrations were normal.

The hypocalcemia resolved after intravenous and oral calcium administration, skin color improved, and she was discharged from hospital at 7 days of age without medication. The plasma calcium and phosphate levels at the time of discharge were 2.25 and 2.42 mmol/L, respectively. Plasma calcium and phosphate concentrations at 4 months and 18 months of age were normal. She remained in good health, except for episodes of otitis media and skin allergy.

At 4 years of age, in 1985, she began to complain of cramps in her hands and feet. The plasma calcium level was 2.01 mmol/L, the ionized calcium level was 1.04 mmol/L, the phosphate level was 1.41 mmol/L, the magnesium level was 0.64 mmol/L, and the PTH level was 31 ng/L (reference range, 10 to 65 ng/L). Immunologic studies yielded normal results.

The patient has been treated with calcitriol since 1987. The plasma calcium levels have been borderline normal to mildly hypocalcemic. Plasma magnesium levels were also mildly low, at 0.53 to 0.64 mmol/L (reference range, 0.70 to 0.95 mmol/L), and the plasma PTH level was 7 to 17 ng/L.

PATIENT 3.—Patient 3 was born December 22, 1970. The bio-

chemical findings and treatment of this female patient are shown in Fig 3. The patient, now 20 years of age, was born at 39 weeks' gestation by cesarean section due to irregular labor. Her birth weight was 3750 g. She had an Apgar score of 2 and required resuscitation and oxygen therapy. Her condition improved promptly. However, she suffered generalized convulsions on the second day of life. The plasma calcium level was 1.55 mmol/L, the magnesium level was 0.95 mmol/L, and the phosphate level was 2.01 mmol/L. No other cause of the seizure disorder was found, and no evidence of cardiac or immunologic abnormalities was found. She had a high-pitched, shrill cry that was later diagnosed as laryngomalacia. Repeated injections of parathyroid extracts increased the plasma calcium concentrations. Maternal plasma calcium and phosphate concentrations were normal. She was treated with 8400 U of vitamin D₂ and oral calcium supplementation.

At 12 months of age, the vitamin D₂ treatment was reduced, and it was stopped completely at age 14 months in 1972. The subsequent course, as shown in Fig 3, indicates that she remained normocalcemic until she was 7 years of age in 1977, when the plasma calcium started to fall below the normal value. Plasma PTH values were either at the lower end of normal or below the normal range. During a trial period of oral calcium supplementation, the plasma calcium level decreased further. Calcitriol therapy, which was started at 10 years of age, has been maintaining the plasma calcium level within the normal range. Plasma PTH concentrations continue to be below normal. In addition to hypoparathyroidism, she has adolescent exogenous obesity and residual hoarseness of the voice.

COMMENT

Substantial hypocalcemia during the early neonatal period is uncommon in full-term normal infants. Most patients with early neonatal hypocalcemia are premature, have birth asphyxia, or are born to diabetic mothers.⁵⁻⁸ All of our patients were born at term with normal birth weights to nondiabetic mothers. Patient 3 had a history of neonatal distress, but her only outstanding problem was related to hypocalcemia.

The hypocalcemia resolved within a week in patient 2, and before 3 and 14 months of age in patients 1 and 3, respectively. These patients would have been diagnosed as having either neonatal hypocalcemia or transient congenital hypoparathyroidism had they not returned with a recurrence of hypocalcemia later in childhood.

It is not difficult to understand the cause of hypocalcemia during the neonatal period. The limited capacity of the parathyroid glands in these infants rendered them unable to respond adequately to decreases in plasma calcium concentration caused by the abrupt cessation of maternal supply of calcium and the accumulation of phosphate load from the endogenous source. It is more difficult, however, to understand what brought about the recurrence of hypocalcemia. Patient 1 had hypocalcemic convulsions following a minor respiratory illness. However, this patient had had symptoms suggestive of hypocalcemia for at least several months before the convulsions. The childhood hypocalcemia developed gradually over several years in patients 2 and 3. It appears that the parathyroid reserve was inadequate to meet the normal demands of childhood.

In all three patients, the PTH levels were either at the low end of or below the normal range, but they were consistently detectable by a sensitive assay. In patient 3 only, PTH levels were measured during the normocalcemic period; the levels were consistently low but were detectable. This patient, and most likely the other two patients, had permanent partial hypoparathyroidism regardless of their plasma calcium concentrations.

Among disorders of calcium homeostasis encountered

during the neonatal period, the DiGeorge syndrome most closely resembles congenital partial hypoparathyroidism as far as the parathyroid function is concerned. A number of reports indicate that the DiGeorge syndrome is heterogeneous and may be partial in immunologic, cardiac, and parathyroid abnormalities.⁹⁻¹¹ The PTH concentrations of the three patients with partial DiGeorge syndrome followed up in our clinic are within the range found in congenital partial hypoparathyroidism reported herein (Fig 4). Mallette et al¹² described four neonates who had transient congenital hypoparathyroidism with anomalies of the pulmonary valve. Our patients had no cardiac or immunologic abnormalities.

Some acquired forms of hypoparathyroidism may also be partial. For example, during the progression of MEDAC syndrome (multiple endocrine deficiency, Addison's disease, and candidiasis), the patient may have partial PTH deficiency (Fig 4). Similarly, in the course of iron storage disease in thalassemia, the patient may go through a phase of partial hypoparathyroidism before developing complete hypoparathyroidism. In these acquired conditions, however, the underlying disease is usually obvious, and the disease involves other organs in addition to the parathyroid gland. In all of these conditions, the degree of PTH deficiency will be better defined in the future, as sensitive assays for plasma PTH measurements become more readily available.^{13,14} It is possible that the patients described herein are unusual examples of patients with transient congenital hypoparathyroidism. We rather believe, however, that partial hypoparathyroidism is a problem shared by all patients with transient congenital hypoparathyroidism, to a greater or lesser degree. There are lessons to be learned from our patients for physicians caring for newborns and children: (1) transient congenital hypoparathyroidism is not always transient, (2) neonatal hypocalcemia may signal permanent partial hypoparathyroidism, and (3) hypocalcemia in an otherwise normal neonate should be followed up with blood calcium measurements during childhood and adolescence.

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Clinic-Based Intervention to Promote Literacy

A Pilot Study

Robert Needlman, MD; Lise E. Fried, MSPH; Debra S. Morley, MA; Sunday Taylor; Barry Zuckerman, MD

● Educational research has shown that children become literate more easily if their parents read to them. A clinic-based program was designed to encourage early book use among parents of children at risk. It included (1) waiting room readers, (2) guidance about literacy development, and (3) provision of children's books at each visit. Seventy-nine parents of children aged 6 to 60 months were interviewed. Parents who had previously received a book were more likely to report looking at books with their children or that looking at books was a favorite activity (adjusted odds ratio, 4.05). This association was strongest among parents receiving Aid to Families With Dependent Children (odds ratio, 7.8). This preliminary study suggests that pediatricians can play a role in enriching children's early literacy environments, especially for children at high risk of school failure.

(AJDC. 1991;145:881-884)

Reading failure disproportionately affects children from socially disadvantaged homes and contributes to the propagation of the cycle of poverty.¹ Pediatricians have a special opportunity to encourage behaviors that improve the child's chances to become literate. Parents come to the clinic regularly throughout their children's early years, and they expect to receive guidance that is important to the well-being of their children. Guidance from the pediatrician occurs within the context of a personal relationship and can be tailored to the individual child and family.

Current research on literacy acquisition assigns a critical role to the child's early literacy environment. Young children learn about the form and function of written language through daily exposure to print mediated by their parents or other adults. The quality of these early experiences affects the child's ability to profit from formal reading instruction once in school.² Thus, interventions that enhance the child's early exposure to literacy may increase the chances of reading success, even in the face of other risk factors associated with poverty.

While a variety of experiences contribute to the preschool child's emerging literacy, there is consensus among researchers that exposure to children's books is particularly important.³⁻⁷ Children who are read to learn that printed words convey information they want to know. This realization motivates them to master reading, a task that, by nature, is repetitious and often frustrating.⁸ Book sharing routines also familiarize children with the question-and-answer format prevalent in elementary schools, smoothing the transition from home-based to school-based learning.⁹

For infants and toddlers as well as preschool children, books provide a context for language and cognitive developments related to literacy acquisition and school success. Rhythmic speaking and holding enhance infant attention.¹⁰ Parents are more responsive to their children's utterances while looking at books together than during free play or play with a toy.¹¹ With repeated "reading," increasingly complex language routines develop, from the simple labeling of objects to descriptions of events to the child's creation of fictions about his or her own experiences relating to the book.¹²⁻¹⁴ As a group, children from underprivileged homes experience fewer of these important book-sharing interactions than do their more advantaged peers.^{2,7} Because of the benefits of early book sharing and the special potential for parent education in the pediatric clinic, we implemented a program in the Pediatric Primary Care Clinic at Boston (Mass) City

Department Editors.—Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—Promotion of literacy is an important national issue, but how can pediatricians be effective in this effort? Needlman et al present a clinic-based program that offers us suggestions that worked. See if you can apply this to your practice.—H.D.A.

Accepted for publication January 14, 1991.

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Read in part before the 31st Annual Meeting of the Ambulatory Pediatric Association, New Orleans, La, May 1, 1991.

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Table 1.—Sample Characteristics (n = 79)

Characteristic	% of Patients
Gender of child	
M	48
Childs age, mo	
6-12	41
>12-24	32
>24-60	28
Parents' country of origin	
United States	49
Haiti	17
Puerto Rico	10
Other	24
Parents' educational level (n = 76)*	
0-8th grade	5
9-11th grade	20
High school graduate	40
Post-high school	36
Government support (n = 77)*	
AFDC	39
No AFDC	61
Marital status (n = 62)*	
Single	40

*Patient numbers are less than 79 due to missing data. AFDC indicates Aid to Families With Dependent Children.

Hospital to promote literacy development by encouraging parent-child book sharing.

The purpose of this pilot study was to assess parental response to the clinic-based literacy program. We hypothesized that exposure to the literacy program would be associated with increased book use by the parents and children.

SUBJECTS AND METHODS

Intervention

The clinic-based literacy program began in March 1989. The program included three components: (1) volunteers who read aloud to children in the waiting room, (2) counseling by the pediatrician about literacy development, and (3) book distribution. The program was designed so that a child would spend time with the reader in the waiting room and then move to the examination room where parent education about literacy development and a free book would be delivered together as part of anticipatory guidance.

Volunteers from the hospital and surrounding community underwent a 1-hour training session that focused on flexibility in approaching children of different ages and interests (eg, not always sticking to the printed text as well as encouraging participation) and supporting positive parental responses (eg, commenting on the child's level of interest). In practice, the content of the reading sessions varied depending on the particular reader, child, and level of activity in the waiting room.

Pediatricians, residents, and nurse-practitioners were trained via a combination of lectures on literacy development and workshops. The workshops focused on ways to support parents' appropriate desire to perceive their children as "smart" without encouraging undue pressure to "learn to read" too early. No set content for the anticipatory guidance was established, and in practice the counseling varied depending on the particular practitioner and family.

A selection of developmentally and ethnically appropriate books was obtained in sufficient quantity that every child from 6 months through 6 years of age could take home a free book after each visit. A stock of books was kept in the clinic for pediatricians to distribute to their patients.

Subjects

Between January and April 1990, parents bringing their children to the Boston City Hospital Pediatric Primary Care Center for routine care were recruited for the study. Parents present in the waiting room during the hours that the interviewer worked were asked to participate. Parents who were conversant in either English or Spanish and whose children were between the ages of 6 and 60 months

were included in the study. Parents were excluded if the children were acutely ill or had not received routine care in the clinic within the past 6 months. Few parents who met the study criteria refused to participate; however, no record of refusals was kept.

Survey Design

The study employed a 15-minute structured interview administered by a research assistant who was not otherwise associated with the literacy program. Respondents consented to answer a series of questions about how their child "spends his/her time." They were not told at the outset that the focus of the questions was literacy, although this was made clear after information regarding the principal outcome had been elicited. The study was approved by the Boston City Hospital Human Investigations Committee.

After demographic data were obtained, parents were asked to provide a 24-hour "activity recall," modeled after a 24-hour diet recall, including everything they did with their child during that period. To increase the recall of details, the day was broken down into three periods: waking to lunch, lunch to dinner, and dinner to bedtime. If parents responded "We played," they were asked to describe what they actually did. Parents were then asked what their child's three favorite activities were, excluding eating and sleeping. These questions were presented in an open-ended format and at a point in the interview when no mention had yet been made of books or reading. Thus, the parents' responses were not likely to have been biased by any tendency to give answers they thought were desirable or expected. "Literacy orientation" was scored as positive if the parent mentioned looking at books or magazines with the child during the past 24 hours or included looking at books among the child's three favorite activities. This measure was designed to reflect parent-and-child behaviors believed to be particularly literacy-promoting and to be least subject to reporting bias.

After these open-ended questions, parents were asked specific questions regarding their use of books with their child and the number of books in the home. Parental reading habits and a history of having been read to during childhood were then assessed. As a way of gauging parental literacy, parents were asked to choose which one of three statements best described their reading ability: (1) "I can read anything easily." (2) "I can read enough to get by." (3) "Reading is difficult for me."

Finally, parents were asked to recall whether during previous visits they had seen the volunteer readers, had spoken with their pediatrician or nurse-practitioner about books or reading, or had been given a free book by their pediatrician or nurse practitioner. Parental report of exposure to each of these components of the literacy program constituted the independent variables for the study. As noted, the actual content of the waiting room reading experience and anticipatory guidance varied depending on the reader, pediatric provider, and family.

Analysis

Because the study was designed to evaluate an ongoing program, we were unable to assign subjects randomly to an intervention or nonintervention group. Instead, we compared parents who reported prior exposure to each of the components of the literacy program with those who denied such exposure. Characteristics of exposed and nonexposed parents were compared to determine whether they were similar. In form, this was a nested case-control design.

Literacy orientation, defined above, was the dependent variable used in both bivariate (unadjusted) and multivariate (adjusted) analyses. χ^2 Tests were used in the bivariate analyses. $P < .05$ was considered statistically significant. A logistic regression analysis (SAS computer program) was used to assess adjusted relationships for the dichotomous outcome. Odds ratios and 95% confidence intervals were calculated from these analyses.¹⁵

RESULTS

Seventy-nine parents participated in the study. Demographic characteristics of the sample appear in Table 1. Thirty-eight percent (30/79) reported having seen a volunteer reader in the waiting room during a previous visit;

Table 2.—Associations Between Exposure to Program Components and Reported Literacy Orientation

Program Component	% Reporting Literacy Orientation
Saw waiting-room reader (n=78)*	
Yes	40
No	42
	P = .9
Guidance on literacy development (n=76)*	
Yes	43
No	42
	P = .9
Received book (n=77)*	
Yes	53
No	32
	P = .06†

*Patient numbers are less than 79 due to missing data.

†Odds ratio, 2.4; 95% confidence interval, 0.95 to 6.1.

27% (21/79) reported having talked with their pediatrician about literacy development; and 46% (36/79) had been given one or more books by their pediatrician. Although the program was designed to incorporate readers, anticipatory guidance, and books, only 6% (5/79) reported having been exposed to all three components of the program. Therefore, each component was considered separately. Parents exposed to the readers, anticipatory guidance, or books did not differ from unexposed parents in any of the following characteristics: child's gender, child's age, parent's country of origin, parent's educational level, government support, or marital status.

Bivariate analyses showed no statistically significant relationships between literacy orientation and exposure to any of the three components of the program, taken singly or in combination. Trends linking exposure to the readers or anticipatory guidance were not evident; therefore, these program components were omitted from subsequent analyses. There was, however, an association between literacy orientation and having been given a book at a previous visit that approached statistical significance (Table 2). Further exploration of this one component (books) was performed.

To assess the independent effect of having been given a book and to control for possible confounding variables, a logistic regression procedure was performed, which included the following: age of the child, parental ethnicity, parental educational level, parental reading habits, government support (whether receiving Aid to Families With Dependent Children [AFDC]), and whether the child had been given a book by their pediatrician. In this model, having been given a book was associated with literacy orientation ($\beta = 1.40$; odds ratio, 4.05; $P = .028$; 95% confidence interval, 1.12 to 14.6). This finding shows that parents who were given books were approximately four times more likely to report literacy orientation than parents who did not receive books, when other factors were controlled for. The fact that the odds ratio increased from 2.4 in the unadjusted analysis (Table 2) to 4.05 in the adjusted analysis indicates the effect of uncontrolled confounders in the unadjusted analysis.

Given the diversity of the sample, further analyses were performed to investigate whether receiving books had a positive effect for a specific subgroup of parents. Three factors were chosen as likely to influence parental response to the intervention: whether the family received AFDC (used as a proxy for income), parental education, and the child's age. Stratified analyses were performed for each of these variables.

Stratification by income revealed a strong effect (Table

Table 3.—Association Between Having Received a Book and Literacy Orientation: Stratification by Income (AFDC Status) (n=77)*

Variable	% Reporting Literacy Orientation
Parents receiving AFDC (n=30)	
Received book	
Yes (n=14)	64
No (n=16)	19
	P = .011 (odds ratio, 7.8)†
Parents not receiving AFDC (n=47)	
Received book	
Yes (n=22)	46
No (n=25)	40
	P = .7 (odds ratio, 1.25)

*AFDC indicates Aid to Families With Dependent Children.

†Confidence interval, 1.48 to 41.2.

3). Among parents receiving AFDC, 64% of those who had been given books reported literacy orientation compared with 19% of those who had not been given books ($P = .011$). Among parents not receiving AFDC, literacy orientation was not significantly different between parents who had or had not been given books (46% vs 40%, $P = .7$). Stratification by parent's education or child's age did not result in significant associations between literacy orientation and having been given a book.

COMMENT

The main finding of our study is that parents who had been given a children's book during a previous visit were approximately four times more likely to report positive literacy orientation, after controlling for confounding factors. This result supports the contention that a simple, inexpensive, clinic-based intervention can lead to positive changes in the home literacy environment, as reported by parents. Such changes may result in increased success in acquiring reading skills in early elementary school. It is encouraging that the benefits of the intervention were especially apparent among families at highest risk for reading failure, ie, those receiving AFDC.

Our findings are consistent with the single other published evaluation of a clinic-based literacy program. In Pittsburgh, the percentage of parents who reported daily reading with their child rose from 47% to 69% 6 months after having been given a packet of books and information by a volunteer in the clinic. However, details of sample selection and data collection were not reported.¹⁶

Several potential sources of error need to be considered in interpreting our findings. First, although the interviewer attempted to enroll all eligible parents, it is possible that parents less responsive to the intervention were missed with greater frequency. This bias would have led to overestimation of intervention effects.

Second, the study relied on parental self-reporting, raising the possibility that observed differences may have reflected parental perceptions or priorities rather than their actual behavior. The possibility of biases introduced because of systematic differences in reporting between groups of parents cannot be excluded. However, information for the principal dependent variable was obtained by spontaneous recall, without the parent knowing the specific purpose of the question.

Third, the fact that patients were not randomized increases the chance that observed associations resulted from confounding. Although several factors likely to be

confounders were included in the logistic regression model, we cannot exclude confounding by unmeasured factors. For example, parents who were more highly motivated to provide literacy stimulation for their children might also have been more vocal in requesting books, which could explain the apparent association between taking home a book and literacy orientation; however, it cannot easily account for the large increase in literacy orientation associated with taking home a book among parents receiving AFDC compared with the negligible increase among parents not receiving AFDC.

Finally, small sample size may have resulted in type II errors in the stratified analyses. It is possible that with larger sample sizes, additional subgroups of parents who responded positively to the program would be identified.

While the present study suggests a positive effect of book distribution on the reported frequency of literacy orientation, similar effects were not found for the volunteer readers or the anticipatory guidance. Parents' ability to remember having seen a volunteer or having spoken about reading with their pediatrician may be more subject to recall bias than whether they were given a book to take home. Some parents may have been affected by the modeling or counseling but may have failed to report the exposures. Another explanation may be that modeling and anticipatory guidance influence the quality of the parent-child book interaction more than they do its quantity. Qualitative aspects of early literacy interactions have been shown to differ between social classes,¹⁷ and such differences may be more important than the mere quantity of book use.

It may be that for the poorest children, the lack of books poses the greatest barrier to literacy-promoting experiences. By supplying books in those homes, we may have been not only communicating the importance of book sharing to parents but also providing them with the means to act on the information. Informal discussions with parents indicate that the books often provided a vehicle for the child to secure parental attention: "He's always bringing me a book to read for him." The fact that the books were given by the pediatrician or nurse practitioner was meaningful to some parents: "Every time I brought her to the clinic, the doctor gave us a book, so I figured he must want me to do something with them."

Future Research

Further work needs to be done to confirm these findings. Future evaluations of clinic-based literacy programs should include randomized, controlled trials employing standardized modeling and pediatric guidance, observation of the parent-child book interaction before and after the intervention, and testing of the child's verbal and written language skills. It will be necessary to follow a group of intervention and control children longitudinally to discover whether early pediatric intervention can indeed affect elementary school performance for children at risk. One published study suggested that preschoolers who are given books do indeed perform better in first grade.⁷

Implications

This preliminary study suggests that the pediatric primary care clinic can serve as an effective site for interventions to enrich children's early literacy development, particularly for those children at greatest risk for school failure. Pediatricians can develop such programs themselves or invite community literacy groups to provide the services and books in the clinic. Medical-educational col-

laborative programs are more likely to meet the needs of children than is either type of intervention alone. Specific support for literacy development may complement other efforts by pediatricians to combat the biologic and social risk factors for school failure.¹⁸

This work was supported in part by grant MCJ 009094 from the Bureau of Health Care Delivery and Assistance, Maternal and Child Health Branch. The Reach Out And Read program was supported by grants from The Old South Church Fund, Boston, Mass, The Polaroid Foundation, Cambridge, Mass, The Francis R. Dewing Foundation, Wellesley, Mass, and Ronald McDonald Children's Charities, Boston-Providence Chapter, Boston, Mass, The Boston Globe Foundation, Boston Mass, and Wordsworth Books, Cambridge, Mass.

We thank Howard Bauchner, MD, for his helpful comments and Kathleen Fitzgerald, MA, for codirecting the literacy program.

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PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

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WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: General: As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

Age (Months)	Reaction	Number of Subjects Evaluated	Dose 1			Number of Subjects Evaluated	Dose 2		
			6 hr	24	48		6 hr	24	48
2-14*	Fever >38.3°C (101°F) Rectal	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F) Rectal	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against *Haemophilus b* disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group (see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792—PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

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Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

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Immunization Response Varies With Intensity of Acute Lymphoblastic Leukemia Therapy

Derry Ridgway, MD; Lawrence J. Wolff, MD; Adamadia Deforest, PhD

• Twenty-four children receiving maintenance chemotherapy for acute lymphoblastic leukemia were given booster doses of tetanus-diphtheria combined toxoids. One month later, 19 of the 24 children were given *Haemophilus influenzae* B oligosaccharide-cross-reacting material conjugate vaccine. Following immunization, all patients had protective antibody titers against tetanus, 92% had protective antidiphtheria titers, and 84% had protective titers against *H influenzae*. Preimmunization titers, postimmunization titers, and response to immunization varied according to the intensity of therapy. There was no correlation with duration of therapy or quantitative hematologic values in the peripheral blood. These observations support the recommendation that children treated for acute lymphoblastic leukemia should be immunized against *H influenzae* B.

(AJDC. 1991;145:887-891)

The role of immunization in the treatment of children receiving chemotherapy for malignant disease remains controversial. Concerns about the persistence of protection provided by previous immunizations and about the efficacy of immunization or reimmunization during chemotherapy make clinical decisions difficult. Few studies have examined antibody titer levels or the response to immunization in this population.¹⁻⁷ Most previously immunized children receiving anticancer chemotherapy have protective antibody titers against both tetanus and diphtheria, and most children respond with fourfold or greater increases after booster immunization. All studies report a few exceptions to these generalizations. Kung and coworkers¹ noted that for both diphtheria and tetanus, antibody levels and response to immunization were lower among children with leukemia than among children receiving chemotherapy for other forms of cancer.

Current approaches to therapy in children with acute lymphoblastic leukemia (ALL), the most common form of childhood cancer, use different intensities of therapy depending on prognostic characteristics.⁸ While some chil-

dren with favorable initial characteristics may be treated with low-intensity chemotherapy, others receive much more aggressive initial therapy, and then receive either continuous or periodic cyclic aggressive therapy. We sought to determine if the intensity and/or duration of therapy was related to the baseline antibody titer or to the response to immunization among children receiving therapy for leukemia. We compared the preimmunization and postimmunization titers against tetanus, diphtheria, and *Haemophilus influenzae* in a group of children receiving chemotherapy for ALL of the "standard" protocol, an "aggressive induction-consolidation with intensification and standard maintenance" protocol, and an "aggressive induction-consolidation with aggressive maintenance" protocol.

MATERIALS AND METHODS

Subjects

Twenty-four children (17 boys and seven girls) receiving maintenance chemotherapy for ALL were entered in the study after permission was obtained in accordance with the requirements of the Human Subjects Research Committee of the Oregon Health Sciences University, Portland. The patients ranged in age from 3 to 13 years (mean age, 7.3 years). Each patient had been immunized in infancy with four injections of diphtheria and tetanus toxoids. Eight patients had received an additional booster dose of both toxoids before school entry and two other patients had received an additional booster dose after the completion of an initial 2- or 3-year course of antileukemic chemotherapy. No patient had been immunized against *H influenzae* B or been treated for known or suspected invasive *Haemophilus* infection.

All subjects were in complete remission at the time of entry, with remission durations ranging from 6 to 35 months (mean remission, 16.2 months). Prognosis (ie, favorable, intermediate, or unfavorable) was determined using the standard criteria of age, white blood cell (WBC) count, morphologic cell features, and mass disease.⁸ Seventeen patients were in first remission of their disease, three patients were in second remission after sustaining marrow relapses while not receiving therapy, one patient was in third remission after sustaining two marrow relapses while not receiving therapy, and two patients were in first continuous marrow remission after sustaining extramedullary relapses treated with local therapy and systemic reinduction.

Six patients were treated with standard therapy protocol (STD); 12 patients were treated with the Children's Cancer Study Group modification of the Berlin-Frankfurt-Munster protocol (BFM)⁸; and six patients were treated with the Children's Cancer Study Group modifications of the New York protocol or the very similar

Accepted for publication April 9, 1991.

From the Department of Pediatrics and the Doernbecher Memorial Hospital for Children of the Oregon Health Sciences University, Portland (Drs Ridgway and Wolff) and St Christopher's Hospital for Children, Philadelphia, Pa (Dr Deforest).

Reprints not available.

Table 1.—Treatment Protocols for Acute Lymphoblastic Leukemia

Stage	Protocol*		
	STD	BFM	NY/L
Induction (weeks 1-4)	Vincristine, L-asparaginase, Intrathecal (IT) methotrexate, prednisone	Vincristine, daunorubicin, L-asparaginase, IT methotrexate, prednisone	Cyclophosphamide, daunorubicin, vincristine, IT methotrexate, prednisone
Consolidation (weeks 5-9)	Prednisone, 6-mercaptopurine, IT methotrexate	Prednisone, 6-mercaptopurine, IT methotrexate, cyclophosphamide, cytosine arabinoside (+/-cranial irradiation)	Prednisone, L-asparaginase, IT methotrexate, carmustine, cytosine arabinoside, cranial irradiation, 6-thioguanine
Maintenance (week 9 through year 2 or 3)	Vincristine, 6-mercaptopurine, IT methotrexate, prednisone methotrexate	Vincristine, 6-mercaptopurine, IT methotrexate, prednisone methotrexate	Vincristine, daunorubicin, IT methotrexate, cytosine arabinoside, 6-thioguanine, prednisone or hydroxyurea, cyclophosphamide, carmustine (+/-)
Reintensification (interrupts maintenance weeks 20-28, BFM only)	...	Vincristine, dexamethasone, 6-thioguanine, doxorubicin, cyclophosphamide, cytosine arabinoside, L-asparaginase	Methotrexate

*STD indicates standard therapy; BFM, Berlin-Frankfurt-Munster; NY/L, New York protocol or LSA2L2; plus sign, with; and minus sign, without.

LSA2L2 (NY/L) protocol⁸ (Table 1). Nine of the patients in the BFM protocol also received cranial irradiation (18 to 24 Gy) during the second month of therapy or during a previous period of therapy, and two patients received spinal irradiation (12 Gy) as well.

Study Design

Immunization histories were recorded and the patients were immunized with diphtheria-tetanus vaccine (diphtheria and tetanus toxoids for pediatric use [DT] for children aged 5 years and younger or tetanus and diphtheria toxoids for adult use [Td] for older children [Connaught Laboratories, Swiftwater, Pa]) on the first day of the study. Twenty-eight days later, 19 subjects were immunized against *H influenzae* B by administration of *H influenzae* B oligosaccharide-cross-reacting material conjugate vaccine (HbOC). Four subjects did not receive the HbOC immunization for reasons unrelated to this study. Serum was obtained immediately before each immunization and 28 days after the HbOC injection, frozen, and stored at -70°C . A complete blood cell count was performed in the clinical laboratories of the Oregon Health Sciences University every time serum was drawn.

Antibody Measurement

Serum antibody titers to tetanus toxin were determined with passive hemagglutination as described by Deforest et al⁹ and Hardegree et al.¹⁰ Antibody titers against diphtheria toxin were determined by toxin neutralization in VERO cells as described by Deforest et al⁹ and Miyamura et al.¹¹ Serum antibodies against capsular polysaccharide polyribosylribitol phosphate were determined with a Farr precipitation assay using radiolabeled antigen.^{12,13}

Statistical Analysis

Comparisons of antibody titers among groups or between the prognostic group and titer level were made using the Kruskal-Wallis H test. Correlations among other values were examined with the Pearson *r* test.

RESULTS

Hematologic Values

The mean total WBC counts and absolute lymphocyte counts (ALCs) for patients receiving standard therapy were $4.4 \times 10^9/\text{L}$ (range, 2.0 to $7.1 \times 10^9/\text{L}$) and $1.3 \times 10^9/\text{L}$ (range, 0.1 to $2.5 \times 10^9/\text{L}$), respectively. The corresponding values for patients receiving the BFM or NY/L protocols were lower, but the differences did not achieve statistical significance. The mean WBC count for patients receiving the BFM protocol was $3.3 \times 10^9/\text{L}$ (range, 1.5 to $7.5 \times 10^9/\text{L}$), and the mean ALC was $0.5 \times 10^9/\text{L}$ (range, 0.1 to $2.5 \times 10^9/\text{L}$). The mean WBC count for patients receiving the NY/L protocol was $4.4 \times 10^9/\text{L}$ (range, 0.2 to $23.7 \times 10^9/\text{L}$), and the mean ALC was 0.7 (range, 0 to $2.6 \times 10^9/\text{L}$). The WBC and ALC levels were similar during the 3-month study period.

Tetanus Antibody Levels

The preimmunization and 28-day postimmunization tetanus antibody titers for the three patient groups are shown in Table 2. All patients had protective tetanus antibody titers (≥ 0.01 U/mL)^{9,14} before immunization with DT or Td. Initial titers for children receiving the BFM protocol were lower than for children receiving STD therapy or the NY/L protocol ($P \leq .005$). Similarly, postimmunization titers were lower for patients in the BFM group ($P \leq .005$). Only seven of 12 patients in the BFM group had a fourfold or greater increase in antibody titers after immunization, in contrast to eight of nine assessable patients in the STD or NY/L groups.

No correlation existed between either the WBC count or ALC and initial titers, postimmunization titers, or antibody changes. Five children had ALC levels below

Table 2.—Response of Patients to Immunization*

Patient No./ Age, y/ Prognosis/ Relapse†	Months Receiving Therapy	Tetanus Antibody Titers (Protective Titers ≥0.01 U/mL)		Diphtheria Antibody Titers (Protective Titers ≥0.1 U/mL)		Haemophilus influenzae Antibody Titers (Protective Titers ≥1.0 mg/L)	
		Pre- immunization	Post- immunization	Pre- immunization	Post- immunization	Pre- immunization	Post- immunization
STD							
1/ 4/ intermediate	10	5	20	2.8	11.2	0.31	8.04
2/ 3/ intermediate	12	5	20	0.7	1.4	0.23	2.25
3/ 6/ intermediate	22	1.25	20	0.7	11.2
4/ 5/ intermediate	12	5	10	1	2	0.13	24.32
5/ 4/ favorable	23	0.31	20	0.02	5.6	0.25	12.23
6/ 3/ favorable	12	0.31	10	0.09	1.4	0.1	4.77
Mean (age, 4.2 y)	15.2	2.8	16.6	0.88	5.46	0.194	10.3
BFM							
7/ 4/ intermediate	20	0.625	10	0.18	2.8	0.1	3.66
8/ 6/ intermediate	26	2.5	20	0.7	2.8	0.1	0.62
9/ 8/ favorable/ testicular relapse	11	0.31	0.16	0.09	0.06
11/ 6/ intermediate	13	2.5	5	2	2.8	0.1	0.1
12/ 4/ intermediate	13	0.31	0.625	0.125	0.125	0.1	0.1
13/ 10/ unfavorable	14	0.31	20	0.25	2.8	0.15	1.15
14/ 12/ intermediate/ two relapses	25	0.16	5	0.045	0.7	0.064	15.44
15/ 4/ unfavorable	25	0.16	2.5	0.015	0.25	0.1	20.02
16/ 13/ intermediate/ one relapse	19	1.25	20	0.35	22.4	0.1	60.66
23/ 6/ intermediate	14	0.16	5	0.0075	0.18	0.21	12.14
25/ 13/ intermediate/ central nervous system	31	5	5	1.4	1.4
26/ 12/ intermediate/ one relapse	35	0.31	0.625	0.01	0.01	10.63	10.16
Mean (age, 8.2 y)	20.5	1.18	7.82	0.43	3	1.14	12.4
NY/L							
17/ 7/ unfavorable	23	10	20	2.8	2.8	0.1	669.28
18/ 8/ unfavorable	19	20	20	1.4	22.4	1.28	64.93
19/ 10/ unfavorable	10	5	20	0.5	0.7	0.1	7.29
20/ 10/ intermediate/ one relapse	15	1.25	20	0.7	11.2	1.63	586
21/ 9/ unfavorable	21	20	20	0.7	0.7
22/ 8/ unfavorable	11	5	20	2.8	5.6
Mean (age, 8.7 y)	16.5	10.2	20	1.48	7.23	0.75	331.8

*The upper limits of laboratory determination for antibody titers were 20 U/mL for tetanus and 22.4 U/mL for diphtheria. Values at or exceeding these limits were averaged as the limit value. The lower limit of detection for diphtheria was 0.0075 U/mL; for *Haemophilus influenzae* it was 0.1 mg/L. Values below these limits were averaged as one half the limit value.

†STD indicates standard therapy; BFM, Berlin-Frankfurt-Munster; and NY/L, New York protocol or LSA2L2.

$0.2 \times 10^9/L$; four were receiving BFM therapy, two of whom had fourfold or greater titer rises, and two of whom did not respond. There was no correlation between the initial titers, postimmunization titers, or titer changes and age, prognosis, or the number of months receiving chemotherapy.

Diphtheria Antibody Titers

The preimmunization and 28-day postimmunization diphtheria antibody titers are shown in Table 2. Prior to immunization, 17 patients (seven of 12 patients in the BFM group, four of six patients in the STD group, and all six

patients in the NY/L group) had protective diphtheria antibody titers (≥ 0.10 U/mL).^{9,14} Three patients in the BFM group and the remaining two patients in the STD group had marginally protective titer levels (between 0.01 U/mL and 0.10 U/mL). Two patients in the BFM group had titers less than or equal to 0.01 U/mL. Patients receiving BFM therapy had lower initial titers than the other patients ($P \leq .02$). There were no significant differences in postimmunization antibody titers or in response to immunization among groups. There was no correlation between WBC count or ALC and initial or postimmunization antibody titers or response to diphtheria toxoid administration.

As with tetanus, two patients in the BFM group with an ALC of less than $0.2 \times 10^9/L$ responded with fourfold or greater increases in antibody titers, and two had no response. The two diphtheria toxoid nonresponders were the same patients as the two tetanus toxoid nonresponders. There was no correlation between age, prognosis, or duration of chemotherapy and initial or postimmunization antibody titers or response to immunization. There was a positive correlation between changes in tetanus antibody titers and changes in diphtheria antibody titers following immunization, whether measured as absolute change in titers ($r = .588$; $P \leq .01$) or as a multiple of the initial titer level ($r = .426$; $P \leq .05$).

H influenzae B Antibody Titers

Preimmunization and 28-day postimmunization *H influenzae* antibody levels for the three groups are shown in Table 2. There were no statistically significant differences among groups for preimmunization or postimmunization antibody titers. As shown, six of the 10 patients in the BFM group and all patients in the STD and NY/L groups had protective titers after immunization.

There was no correlation between age, prognosis, WBC count, ALC, or duration of therapy and initial or postimmunization antibody titers or response to immunization. The response to HbOC immunization did not correlate with the response to DT or Td.

COMMENT

The 24 leukemic children examined in this study all had protective antibody levels against tetanus. The protective levels were presumably established during the initial series of infant immunizations and were preserved in many cases without the booster effect of a fifth immunization for as long as 10 years. This observation agrees with the reports by Nyerges et al,³ who found protective titers in all 10 leukemic children receiving chemotherapy and in seven leukemic children after elective discontinuation of chemotherapy, and van der Does-van den Berg et al,⁴ who observed protective titers in 48 of 49 leukemic children at the end of 2 to 3 years of chemotherapy. Twenty-two of the 24 children described in the present study had at least marginally protective titers against diphtheria, an observation similar to that of van der Does et al,⁴ who observed protective titers in 48 of 49 leukemic children at the end of chemotherapy, and Kung et al,¹ who examined 12 leukemic children receiving chemotherapy and found seven with protective titers, four with marginal titers, and one with no detectable antibody. Only three of 20 children in this study developed anti-*H influenzae* antibody titers before immunization. Weisman et al⁶ found that five of 21 leukemic patients receiving chemotherapy had anti-*H influenzae* antibody titers greater than or equal to 1.0 mg/L before immunization. With a lower standard for protection (150 mg/L), Feldman et al² reported that 12 of 34 leukemic children receiving chemotherapy had a protective level before immunization against *H influenzae*.

Following immunization, 100% of subjects had protective titers against tetanus, 92% had protective titers against diphtheria, and 84% had protective titers against *H influenzae*. Nineteen of 21 assessable patients responded to tetanus toxoid by at least a doubling of antibody titers, and 17 of 19 patients responded to HbOC with at least a doubling of measurable titers, but only 16 of 24 patients responded to diphtheria toxoid. In comparison, 25 (86%) of

29 previously described leukemic children (data combined from the reports of Nyerges et al³ and Kung et al¹) responded to tetanus toxoid booster, 60% of previously described leukemic children responded to immunization against *H influenzae*,^{2,6,7} and 83% of previously described leukemic children responded to diphtheria booster immunization.¹ While increases in antibody titers in children with protective levels are of immunologic relevance, they have no known clinical significance. We were unable to observe a statistically significant correlation between total WBC count or ALC on the day of immunization and the response to immunization, although the two children who did not respond to either tetanus or diphtheria toxoid had an ALC of less than $0.2 \times 10^9/L$. In contrast to the report by Feldman et al,² we found no relationship between duration of therapy and antibody levels or response to immunization.

We hypothesized that differences in chemotherapy regimens might be reflected in differences in baseline antibody levels and in response to booster doses of DT vaccine or HbOC. We observed that patients treated with more aggressive induction and consolidation therapy, late intensification therapy, and then continuous standard-dose maintenance therapy (BFM) had lower baseline antibody titers for both diphtheria and tetanus and were less likely to respond to immunization with each of the three agents than patients receiving STD therapy. Patients treated with aggressive induction and consolidation followed by cyclic high-dose maintenance therapy (NY/L) had intermediate values.

Although the precise explanation for these differences remains unclear, it may be that aggressive induction therapies cause a more profound defect in the antibody-forming mechanisms of the immune system. Cyclic maintenance regimens may permit sufficient time for recovery, while the less intense but continuous maintenance regimens do not.

Thirteen of 16 unprotected leukemic children achieved titer levels greater than 1.0 mg/L 1 month after immunization with HbOC. This success rate is slightly higher than that previously reported.^{2,6,7} The difference may be due to increased immunogenicity of HbOC in comparison with previous immunizing agents or to differences in chemotherapy protocols. Our patients were all older than 3 years, older than the patients in the study by Lange et al⁷ but similar to the populations described by Feldman et al² and Weisman et al.⁶ We failed, as did Lange et al,⁷ to confirm the observation by Feldman et al² that longer durations of chemotherapy correlated with lower baseline titers or with poorer response to immunization. Although the number of subjects in this study was small, the results suggest that patients receiving the BFM protocol respond less well than other leukemic children to HbOC immunization.

Several clinically relevant conclusions can be drawn from these results. The presumption that previously immunized leukemic children receiving chemotherapy have antibody protection against both tetanus and diphtheria is supported. This appears to be true even for children who completed only part of their initial immunization schedule before the discovery and initiation of therapy for leukemia. The majority, but not all, of such children will respond to booster immunization with tetanus or diphtheria toxoids. Thus, the "routine" use of DT or Td immunization, as suggested by Nyerges et al,³

cannot be depended on to boost immune status. This caution is particularly applicable to children treated with protocols modeled after the BFM regimen.

The risk of invasive *H influenzae* disease among children treated for acute leukemia (up to 5% of bacteremic episodes^{6,15,16}), the low rate of naturally acquired immunity, and the 84% efficacy of immunization with HbOC support the recommendation that all leukemic children should be immunized against *H influenzae* during therapy.¹⁷ Clinicians should be aware that immunization is not uniformly effective in this population and that invasive *H influenzae* remains a risk, particularly for leukemic patients receiving BFM-like protocols.

The authors gratefully acknowledge the generous support of Praxis Biologics Corp, Rochester, NY, which provided the HbOC vaccine and performed the *Haemophilus influenzae* antibody studies; the assistance of Anita R. Gessner, MS, who performed the diphtheria and tetanus antibody titer tests; and Rosemary Allen, who prepared the manuscript.

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Bullous Eruption in an Infant

A. J. G. McDonagh, MB, ChB, MRCP; A. G. Messenger, MD, MRCP;
B. L. Priestly, MD, BS, FRCP
(*Arch Dermatol*. 1991;127:1049)

Vesiculopapular Eruption in an Infant

Jay M. Weitzner, MD; Marti J. Rothe, MD;
Lawrence Schachner, MD; Edwin Gould, MD
(*Arch Dermatol*. 1991;127:1049)

Diffuse Papular Eruption With Swelling of Joints in a Preschooler

Francine Bruyneel-Rapp, MD, Susan B. Mallory, MD
(*Arch Dermatol*. 1991;127:1049)

Immunogenicity of Tetravalent Rhesus Rotavirus Vaccine Administered With Buffer and Oral Polio Vaccine

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● Between January and November 1989, we studied 174 infants aged 6 to 16 weeks in a randomized clinical trial to (1) determine the immunogenicity of a single dose of tetravalent rhesus rotavirus vaccine (RRV-TV) when administered with three different buffer regimens: no antacid buffer and small-volume (2.5-mL) and large-volume (30-mL) antacid buffer; and (2) examine the potential interference of RRV-TV on the immune response to oral polio vaccine. Immunogenicity of RRV-TV, measured as a fourfold rise in antibody titers to rotavirus, was similar in the groups receiving small- and large-dose buffer (45% and 49%, respectively) and significantly less in the group that received RRV-TV alone (23%). Administration of RRV-TV with oral polio vaccine did not significantly interfere with the neutralization response of oral polio vaccine poliovirus serotypes 1, 2, or 3, and overall, 29%, 87%, and 24% of the infants had a fourfold rise in titer to each serotype, respectively.

(AJDC. 1991;145:892-897)

Worldwide, rotavirus (RV) is one of the most important causes of severe dehydrating diarrhea and vomiting in infants and children.^{1,2} Many researchers have emphasized the need for a vaccine that can be incorporated into routine childhood immunization programs.^{2,3} Several vaccines have been developed and tested that have shown promising results in small field trials.⁴⁻⁷ One, the oral tetravalent rhesus rotavirus vaccine (RRV-TV), has advanced to a large-scale trial at 22 centers in the United States involving nearly 1000 infants who are receiving three oral doses. If this trial demonstrates signif-

icant efficacy, this vaccine might be considered for incorporation into routine childhood immunization programs in the United States.

In vaccine studies conducted to date, RV vaccines have been administered with large volumes of buffer and separated by periods of 2 weeks from oral poliovirus vaccine (OPV) immunization. Each of these conditions would make the incorporation of RV vaccine into the routine schedule of childhood immunizations logistically difficult: administration separate from that of the OPV would require extra visits, and the large-dose buffer is more difficult to administer than the vaccine itself. In previous studies, buffer was shown to be important to ensure a good immunogenic response, but the dose of buffer has never been titrated against the immunogenicity of the RRV-TV vaccine to determine if a smaller dose would have a comparable effect.⁸ Furthermore, since rotavirus vaccine should optimally be administered before 2 to 3 months of age, it could ideally be given together with OPV if there were no interference in the immunogenicity of either vaccine. This issue has been addressed in previous studies⁹⁻¹² but has not been adequately resolved.

This study was conducted (1) to determine the immunogenicity of RRV-TV vaccine when administered with one of three different buffer regimens (large-volume [30-mL], small-volume [2.5-mL], and no buffer) and (2) to examine the interference of RRV-TV in the immune response to OPV.

SUBJECTS AND METHODS

Subjects

The study was conducted at five well-baby and immunization clinics of the DeKalb County Board of Health, Decatur, Ga, during the period between January and November 1989. Healthy infants 6 to 16 weeks of age who came to the clinic for their first well-baby visit and immunization (diphtheria-pertussis-tetanus and OPV) were recruited into the study. A pediatrician or study nurse reviewed each infant's medical history and examined the child. Infants were excluded if they (1) had had diarrhea, vomiting, or fever within the past week, (2) had been exposed to chickenpox within the past 3 weeks, (3) had had any serious illness since birth, (4) lived in a home with no telephone, or (5) had anyone in the household who was pregnant or immunocompromised. The study was explained to parents, and written informed consent was obtained. The study was approved by the Human Investigations Committee of Emory University, School of Medicine, Atlanta, Ga, by the Human

Accepted for publication January 3, 1991.

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Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the US Department of Health and Human Services.

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Table 1.—Characteristics of Participants in Four Study Groups*

Characteristic	No. (%)				Total (N = 174)
	RRV-TV/OPV, No Buffer (N = 44)	RRV-TV/OPV, Small Buffer (N = 44)	RRV-TV/OPV, Large Buffer (N = 47)	OPV Alone (N = 39)	
Age, wk					
7-8	7 (16)	15 (34)	10 (21)	11 (28)	43 (25)
9-10	26 (59)	16 (36)	25 (53)	18 (46)	85 (49)
≥11	11 (25)	13 (30)	12 (26)	10 (26)	46 (26)
Sex					
M	23 (52)	27 (61)	28 (60)	22 (56)	100 (57)
F	21 (48)	17 (39)	19 (40)	17 (44)	74 (43)
Race					
W	4 (9)	7 (16)	5 (11)	3 (8)	19 (11)
B	37 (84)	33 (75)	42 (89)	35 (90)	147 (84)
Other	3 (7)	4 (9)	0 (0)	1 (3)	8 (5)
Birth weight, g					
<2500	4 (9)	3 (7)	3 (6)	2 (5)	12 (7)
≥2500	40 (91)	41 (93)	44 (94)	37 (95)	162 (93)
Breastfed					
Yes	5 (11)	6 (14)	5 (11)	4 (10)	20 (11)
No	39 (89)	38 (86)	42 (89)	35 (90)	154 (89)

*Infants who had preimmunization and postimmunization serum samples tested for rotavirus antibodies. There was no significant difference among study groups for the characteristics tested (by χ^2 or Fisher's Exact Test). RRV-TV indicates tetravalent rhesus rotavirus vaccine; OPV, oral polio vaccine.

Research Review Board of Georgia Department of Human Resources, and by the Institutional Review Board for Human Subjects of the Centers for Disease Control, Atlanta.

Study Design and Vaccine Administration

Participants were assigned to one of four groups according to a prepared randomization schedule and enrolled by the study nurse immediately after receiving their first OPV and diphtheria-pertussis-tetanus immunizations. The clinical trial was not blinded because of the difference in volumes of the buffer used and because the group receiving OPV alone did not receive a placebo. At the same time, and to avoid any possible biases, the study nurses who monitored adverse reactions did not know the vaccine group to which each child had been assigned. The laboratory staff who measured immune response to the vaccines received numbered specimens only.

In three of the four groups, infants received RRV-TV with no buffer (group 1), with a small volume of buffer (64 mg of sodium bicarbonate plus 24 mg of sodium citrate in 2.5 mL of water) (group 2), or with a large volume of buffer (400 mg of sodium bicarbonate in 25 mL of soybean formula [Prosobee; Mead Johnson Nutritional, Evansville, Ind]) (group 3). The buffer doses were chosen empirically. The large dose had been administered in most previous trials with the rhesus RV vaccine. The smaller buffer (with citrate) had been successfully used in the oral cholera vaccine trials in Bangladesh⁸ and was theoretically preferred because it produced more prolonged buffering without the reflex stimulation of stomach acid (David Sack, MD, oral communication, January 23, 1991). A control group received no RRV-TV (group 4). In groups 2 and 3, the antacid was administered 5 minutes before RRV-TV. All parents were instructed not to feed their infants for 1 hour before and 30 minutes after immunization. The infants remained in the clinic for approximately 30 minutes after vaccination for evaluation of any immediate reactions.

To monitor the immune responses to RRV-TV and OPV, the nurse collected blood samples on the day of and 56 days after vaccine administration. Serum samples were inactivated at 56°C for 30 minutes and stored at -20°C until analyzed.

Vaccine

The RRV-TV was prepared by Wyeth-Ayerst Research, Philadelphia, Pa, and contained the rhesus RV serotype 3 strain and genetic reassortants for human serotypes 1, 2, and 4.⁴ The vaccine was stored at 2°C to 8°C as a lyophilized product and was reconstituted immediately before use. Each 1.0-mL dose of oral RRV-TV consisted of 10 000 plaque-forming units (PFU) of the parent rhesus RV and each of the three reassortant strains (total, 40 000 PFU).

Surveillance for Adverse Reactions

After the administration of RRV-TV, parents received a digital thermometer, a bottle of oral rehydration solution, and acetaminophen drops to treat fever resulting from the diphtheria-pertussis-tetanus vaccine, a Board of Health recommendation at that time. The parents were instructed on how to take the infant's rectal temperature.

For the 5 days after vaccination, parents were instructed to record in a structured diary the infant's afternoon temperature and the occurrence of loose stools or vomiting. For the 2-month period after vaccination, they were instructed to call the study nurse if the infant became ill, had loose stools, or developed diarrhea, defined as three or more stools judged to be looser than normal in a 24-hour period.

The nurse contacted the parent by telephone every other day and reviewed the signs or symptoms reported. For any problems, including diarrhea, the nurse made a home visit to evaluate the infant's condition, collected a stool specimen, and, when necessary, referred the parent to a physician.

RV Antibody Assay

IgA and IgG serum antibodies to RV were measured by enzyme-linked immunosorbent assay, by means of a procedure modified from that described previously.⁹ Serum samples were tested in an initial dilution of 1:25, and alkaline phosphatase conjugate (Kierkegaard and Perry Laboratory, Gaithersburg, Md) replaced the peroxidase conjugate used before. Seroconversion was measured as a fourfold or greater rise in titer between preimmunization and postimmunization serum samples.

Polio Antibody Testing

Serum antibodies to poliovirus serotypes 1, 2, and 3 were measured by a microneutralization test^{13,14} in which (1) twofold serial dilutions starting at 1:8 were performed, (2) 25 μ L of HeLa cells at 300 000 cells per milliliter was added to the wells, and (3) 25 μ L (100 times median tissue culture infective dose) of Sabin 1, 2, and 3 poliovirus was dispensed into plates. Seroconversion was defined as a fourfold or greater increase in titers between preimmunization and postimmunization serum samples.

Data Analysis

To evaluate the immunogenicity of RRV-TV with different doses of buffer and to examine the immune response to OPV, we compared the rates of seroconversions and plotted the cumulative distributions of rises in titer to polio (serotypes 1 through 3) and RV IgA and IgG titer rises for each of the study groups. We estimated that rates of seroconversion to RV in the range of 30% to 70% would be needed to demonstrate a statistically significant effect of the buffer. We anticipated rates of seroconversion to poliovirus serotypes 1, 2, and 3 to range from 10% (se-

rotype 3) to 90% (serotype 2), allowing assessment of interference most sensitively with serotype 2. Fisher's Exact Test and χ^2 test were used to test the statistical significance of differences in seroconversions, and the Kolmogorov-Smirnov test was used to examine differences in the cumulative frequency distribution of titer rises between groups.

RESULTS

Characteristics of Participants

Between January 12 and August 31, 1989, a total of 174 infants recruited into the study were monitored for the full 2 months of follow-up and provided serum samples of sufficient quantity for analysis. Of these, 49% were between 9 and 10 weeks of age, 57% were male, 84% were black, 11% were breastfed, and only 7% were of low birth weight (<2500 g) (Table 1). The four groups did not differ significantly by age, sex, race, birth weight, or feeding status.

Table 2.—Clinical Reactions Within 5 Days of RRV-TV Vaccination in Four Study Groups*

Clinical Reaction	No. (%)			
	RRV-TV/OPV, No Buffer (N = 44)	RRV-TV/OPV, Small Buffer (N = 44)	RRV-TV/OPV, Large Buffer (N = 47)	OPV Alone (N = 39)
Temperature, °C†				
≤38.0	34 (80)	39 (89)	42 (93)	33 (92)
38.1-39.0	7 (16)‡	5 (11)	2 (4)	1 (3)
≥39.1	2 (5)	0 (0)	1 (2)	2 (6)
Vomiting				
None	43 (98)	39 (89)	40 (85)	38 (97)
Once or more	1 (2)	5 (11)	7 (16)§	2 (5)
Loose stools, No./d				
≤2	41 (93)	38 (86)	40 (85)	36 (92)
≥3	3 (7)	6 (14)	7 (15)	3 (8)
Watery stools				
None	42 (95)	42 (95)	45 (96)	37 (95)
Once or more	2 (5)	2 (5)	2 (4)	2 (5)

*RRV-TV indicates tetravalent rhesus rotavirus vaccine; OPV, oral polio vaccine.

†There were 1, 0, 2, and 3 infants with unknown temperatures in the four groups, respectively.

‡P = .06 vs group receiving OPV alone, by Fisher's Exact Test.

§P = .06 vs group receiving RRV-TV/OPV with no buffer, by Fisher's Exact Test.

Table 3.—Infants in Each Study Group With Fourfold Rise in Serum IgA and IgG Titers*

Serum IgA/IgG	No. (%)			
	RRV-TV/OPV, No Buffer (N = 44)	RRV-TV/OPV, Small Buffer (N = 44)	RRV-TV/OPV, Large Buffer (N = 47)	OPV Alone (N = 39)
IgA	10 (23)†	20 (45)‡	23 (49)‡	5 (13)
IgG	5 (11)	7 (16)§	7 (15)	1 (3)
Both IgA and IgG	2 (5)	6 (14)	6 (13)	1 (3)
Either IgA or IgG	13 (30)†	21 (48)‡	24 (51)‡	5 (13)

*RRV-TV indicates trivalent rhesus rotavirus vaccine; OPV, oral polio vaccine.

†P < .05 vs groups receiving RRV-TV/OPV with buffer (small or large), by χ^2 test.

‡P < .005 vs group receiving OPV alone, by χ^2 test.

§P = .06 vs group receiving OPV alone, by χ^2 test.

||No IgG titer available for one specimen.

Side Effects of RRV-TV

Clinical reactions were recorded for 5 days after administration of RRV-TV and/or OPV (Table 2). No serious adverse reactions were reported by parents or physicians af-

ter vaccination in any of the study participants, and none of the children was hospitalized. The rate of minor adverse reactions in the total study group was low, and, except for a minor increase in vomiting among the infants receiving RRV-TV with large buffer, no significant differences were observed between groups. Nonetheless, children receiving RRV-TV with buffer tended to have more vomiting and loose stools, although reaction rates were so low that a much larger sample would have been required to look for significance.

Seroresponse to RRV-TV Vaccine

The IgA seroconversion rate for infants receiving small-volume buffer with RRV-TV was comparable with that for infants receiving large-volume buffer (45% and 49%, respectively) (Table 3). These seroconversion rates were significantly higher than those for infants receiving RRV-TV with no buffer (23%) or OPV alone (13%). The difference in seroconversion rates between the group receiving RRV-TV with no buffer and that receiving OPV alone was not statistically significant.

The cumulative frequency distributions of fold rises in IgA and IgG titer were plotted for each of the study groups (Fig 1). Seroconversions of IgA were significantly more common among the groups receiving some buffer. The addition of IgG added little to the overall rates of seroconversion.

Five (13%) of the infants in the control group showed IgA seroconversion, indicating possible exposure to natural RV infection during the study period (Table 3). One of them had an IgA titer rise from 50 to 800, an IgG titer rise from 400 to 1600, and a stool specimen collected for diarrhea 7 days after OPV vaccination that was positive for RV by enzyme-linked immunosorbent assay. Assuming a 16-fold rise in IgA and a postvaccination IgA titer of 800 or higher to represent possible infection with wild-type RV, one infant each in the groups receiving no buffer, small buffer, and OPV alone met these criteria. These cases were not excluded from subsequent data analyses.

Effect of Breastfeeding and Maternal Antibody

Since breastfeeding may interfere with the response to RV vaccines, we compared rates of seroconversion by breastfeeding status combining all RV vaccine groups. Seroconversion by IgA was observed in 38% (6/16) of infants who were breastfed and 39% (47/119) of those who were not breastfed (χ^2 , not significant).

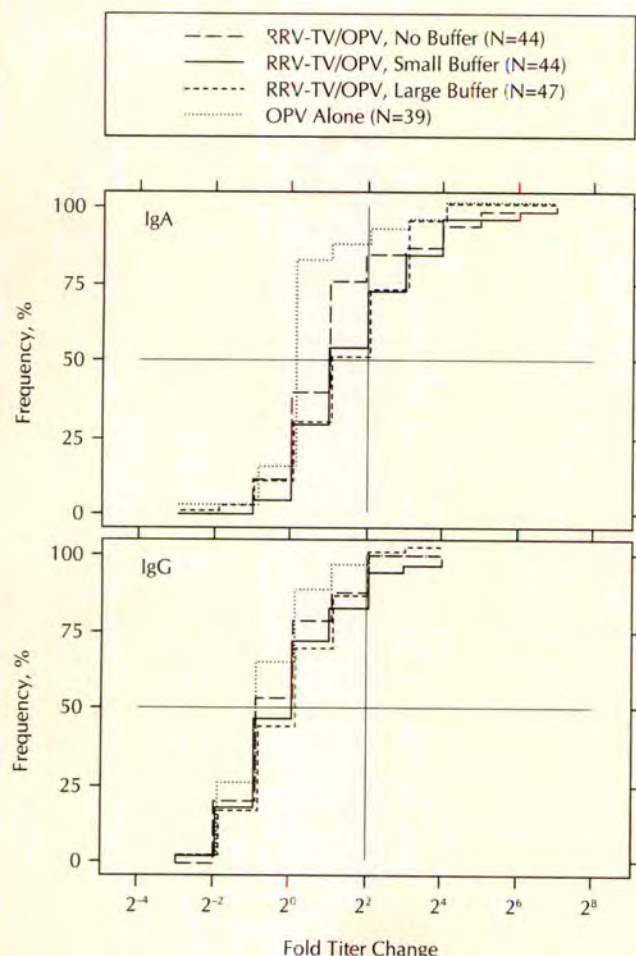


Fig 1.—Cumulative distributions of IgA and IgG titer fold changes in each study group. Vertical line denotes fourfold rise in titer. Horizontal line represents median for the groups. Increased immunogenicity of tetavalent rhesus rotavirus vaccine (RRV-TV) is reflected as a shift in the curve to the right compared with the curve for oral polio vaccine (OPV) alone. Groups that received RRV-TV with small or large buffer had significantly greater titers than the control group ($P < .01$) and the group that received no buffer ($P < .05$) (Kolmogorov-Smirnov test).

Table 4.—Infants in Each Study Group Demonstrating Fourfold Rise in Serum Neutralizing Antibody to Three Serotypes of Poliovirus*

Serotype	No. (%)				Total (N = 142)
	RRV-TV/OPV, No Buffer (N = 39)	RRV-TV/OPV, Small Buffer (N = 34)	RRV-TV/OPV, Large Buffer (N = 38)	OPV Alone (N = 31)	
Poliovirus 1	17 (44)†	8 (24)	8 (21)	8 (26)	41 (29)
Poliovirus 2	35 (90)	27 (79)	35 (92)	27 (87)	124 (87)
Poliovirus 3	9 (23)	9 (26)	7 (18)	9 (29)	34 (24)

*RRV-TV indicates tetavalent rhesus rotavirus vaccine; OPV, oral polio vaccine.

† $P < .05$ vs group receiving RRV-TV/OPV with large buffer, by χ^2 test.

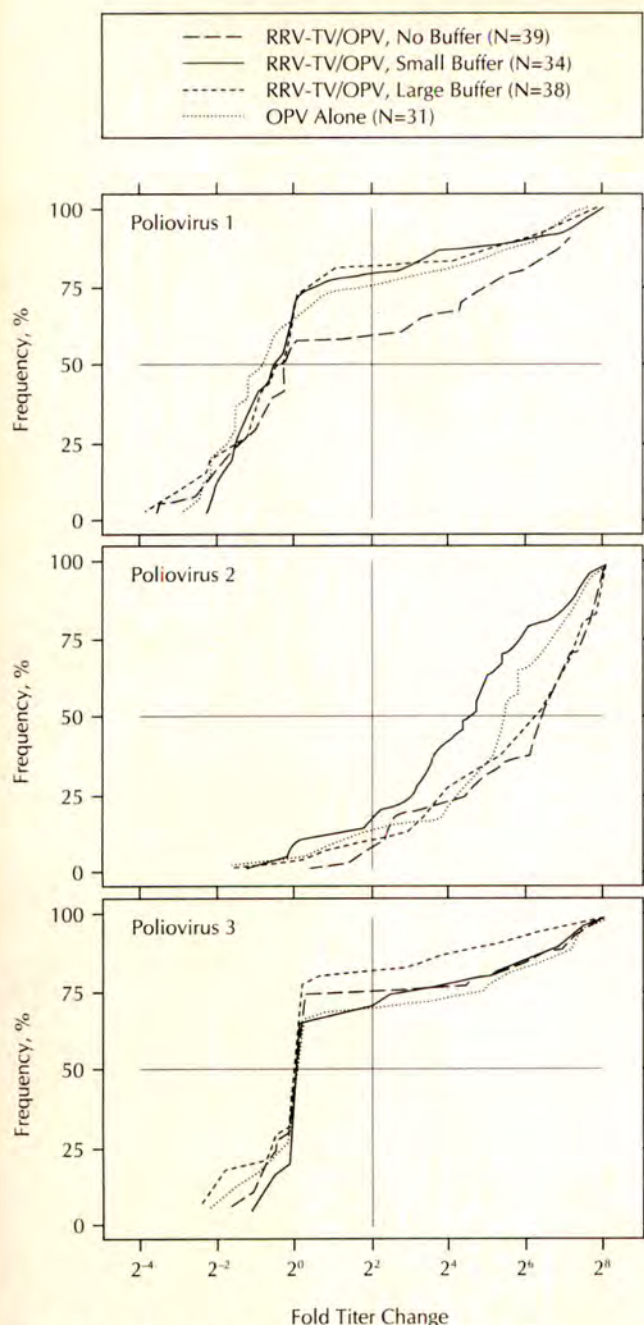


Fig 2.—Cumulative distributions of titer fold changes in serum neutralizing antibody to three serotypes of poliovirus in each study group. Interference by tetravalent rhesus rotavirus vaccine (RRV-TV) in the immune response to poliovirus would be represented by a shift in the group's curve to the left compared with the curve for oral polio vaccine (OPV) alone. We hypothesized that if interference occurred, it would be greatest in the groups that received rotavirus vaccines with the small or large buffer (in which the immune response to rotavirus vaccine was greatest) and would be present for each of the serotypes of OPV used in the neutralizing assays. No consistent or significant trends in the immune response to poliovirus was observed according to the dose of buffer administered with the RRV-TV or for individual poliovirus serotypes used for neutralization.

We also examined whether maternal antibody measured as the infant's initial IgG titer was associated with seroconversion by IgA. Seroconversion was observed in 38% (27/72) of infants with a low initial IgG titer (≤ 800) vs 36% (26/73) of infants with a high initial titer (≥ 1600) (χ^2 , not significant).

Lack of Interference of RRV-TV With the Immune Response to OPV

Polio titers were available for 142 infants whose serum was collected at the time of OPV immunization and 8 to 10 weeks later. Overall, 29%, 87%, and 24% of infants had a fourfold rise in serum neutralizing antibodies to poliovirus serotypes 1, 2, and 3, respectively (Table 4). The differences between the groups receiving RRV-TV/OPV and OPV alone were not statistically significant by χ^2 test. To look for smaller differences or more subtle interference of RRV-TV with the immune response to polio, we plotted the cumulative frequency distribution of fold rise in antibody titer to each vaccine study group (Fig 2). If RRV-TV interfered with the immune response to OPV, we would expect to see a shift in the distribution curve to the left, with a greater shift for the groups receiving small- and large-dose buffer compared with the group receiving RRV-TV with no buffer. Overall, no major differences in the frequency distribution were observed. To the contrary, the group that received RRV-TV with no buffer tended to have higher fold rises to poliovirus 1 than did the other groups.

We hypothesized that perhaps infants who responded poorly to OPV might respond poorly also to RRV-TV. To test this hypothesis, we examined the rates of IgA seroresponse to RRV-TV by rates of neutralizing antibody to polio virus serotypes 1, 2, and 3. When the 72 infants in the two groups receiving buffer were combined, the proportions of infants with seroconversion to both RRV-TV and poliovirus were 31%, 37%, and 50% for poliovirus serotypes 1, 2, and 3, respectively. The proportions of infants with seroconversion to RRV-TV but not poliovirus were 43%, 60%, and 38%. The differences between the corresponding proportions were not statistically significant.

COMMENT

The need for an RV vaccine for children in both developing and developed countries is well documented.^{3,9} For this vaccine to be incorporated into the routine schedule of childhood immunization, it must (1) not interfere with other vaccines, principally OPV, and (2) be easy to administer and not require a large volume of antacid (30 mL). This study demonstrates that antacid is important for achieving a good immune response to the RRV-TV vaccine and that the small (2.5-mL) dose of antacid, which is easy to administer, is as effective as the large volume of antacid, which would be difficult and logistically impractical for use in immunization programs. The addition of a small amount of buffer made a striking difference in immunogenicity of RRV-TV, but the vaccine was essentially non-immunogenic in the group that received no buffer, suggesting that the original estimates of the amount of acid produced in the infant stomach were excessive.^{8,15} Only half of the children who received RRV-TV with buffer had an immune response as measured by IgA and IgG. The extreme sensitivity of the vaccine to acid might be overcome by giving a larger inoculum of the vaccine, multiple doses of the same vaccine, or both. In fact, when this study was initiated, many investigators believed that one dose of the vaccine should be sufficient and that a 40 000-PFU inoculum would be adequate. In more recent trials, a three-dose regimen has been adopted to increase immunogenicity and to improve the potential efficacy of the vaccine. In two of these efficacy trials, the inoculum dose was increased to 400 000 PFU.

Second, this study demonstrates that RRV-TV in its current formulation (40 000 PFU) administered within 1 hour of OPV does not interfere with the immune response to OPV. In most field trials to date, the administration of RV vaccines has been separated from OPV by an interval of at least 2 weeks, in part because of theoretical concerns about the possible interference of these two live oral vaccines. This concern may be unwarranted, since OPV will remain in a child's gut for weeks and be shed by a majority of children for 1 month after first immunization. Also, polio and RV attack different cells in the gut, so interference at the level of cellular attachment or receptors is unlikely. This lack of interference would have to be reassessed if a higher inoculum of RRV-TV were used in future formulations.

The results of this study confirm and extend those of two earlier studies that examined the possible interference of the monovalent RV vaccines and OPV. In a previous study in Atlanta,⁹ blood drawn at 3 to 4 weeks to monitor response to RV vaccines demonstrated an incomplete immune response to OPV. Since immune response to OPV peaks at 6 to 8 weeks, we tested convalescent-phase serum at 8 weeks to maximize our ability to detect a complete response to OPV. As expected, we observed a higher rate (87%) of seroconversion to poliovirus 2 (measured in the same laboratory) compared with 60% reported in the previous study.

In this study we also compared the cumulative distribution of titer rises between groups, a more statistically robust method to look for small differences; none was observed. Moreover, small differences in the immune response to polio that might be missed here would potentially be eliminated with the second or third doses of OPV. Consequently, in future trials, RRV-TV in its current formulation can be given safely with OPV without fear of interference in the immune response to OPV.

We did not examine whether OPV might interfere with the immune response to RRV-TV. This was observed with the RIT 4237 vaccine^{10,12} but could not be demonstrated in our previous trial with monovalent RV vaccines.^{9,16} Considering that most children who receive OPV have poliovirus in their intestines for long periods, the ability to test this interference would require trials substituting inactivated poliovirus vaccine for OPV or delaying the administration of the first OPV immunization, neither of which could be conveniently or ethically examined in our setting.

Although this trial could not be completely blinded, special attention was paid to ensure proper randomization in assignment to groups, to biases in assessing side effects, and to blinding in performing the laboratory studies. Randomization did ensure that the characteristics of the participants in the four study groups were not different, and rates of clinical reactions among vaccinees were so low that a very large sample would have been required to observe significant differences from the control group if they were present. Laboratory specimens were run in bulk without regard to the individual infants' vaccine group.

Some of the recruitment for this trial occurred during the RV season, and 13% of the infants who received no RRV-TV had an immune response to RV. In one such infant, a wild-type infection was documented during the week after enrollment. The infant's immune response to this infection was unlike that of the routine vaccinees, since he had a very large 16-fold rise in IgA, his convalescent-phase IgA titer was unusually elevated

(800), and he had a fourfold rise in IgG (400 to 1600). Using the first two criteria (ie, 16-fold rise in IgA and convalescent IgA titer ≥ 800), we estimated that three infants in the study may have had wild-type infections. The marked difference in the immune response to wild-type infection vs the vaccine suggests that the vaccine may still require a more immunogenic combination of antigens. Wild-type infection is a far better immunogen than oral RRV-TV, and whether the reduced immunogenicity of oral RRV-TV results in reduced protection against symptomatic infection remains to be determined.

This study was funded in part by Wyeth-Ayerst Research.

We acknowledge the support and assistance provided by Paul J. Wiesner, Lynne McIntyre, Bob Davies, Jenine Clifford, Rebecca Gerard, Rachel Cowley, Barbara Hester, Georgina Howard, Betty Jones, Beverly Waters, Claudette Williams, and the nursing staff at the clinics of the DeKalb County Board of Health.

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Response of 7- to 15-Month-Old Infants to Sequential Immunization With *Haemophilus influenzae* Type b-CRM₁₉₇ Conjugate and Polysaccharide Vaccines

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● **Objective.**—To evaluate the immunologic potential of infants 7 to 15 months of age to respond to *Haemophilus influenzae* type b polysaccharide vaccine following immunization with *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine.

Study Design.—One hundred seventy-one infants, aged 7 to 15 months, were consecutively and alternatively assigned to one of three immunization protocols. Group 1 (n=71) received three doses of *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine, group 2 (n=47) received two doses of *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine followed by one dose of *H influenzae* type b polysaccharide vaccine, and group 3 received one dose of *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine followed by two doses of *H influenzae* type b polysaccharide vaccine. Immunizations were given on day 0 and at 2 months and 6 months. Anti-*H influenzae* type b polysaccharide antibody levels were measured on day 0 and 2, 3, 6, 7, and 12 months after the study began.

Results.—*Haemophilus influenzae* type b polysaccharide vaccine given as a second dose stimulated an antibody rise but did so less effectively than *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine. Two doses of *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine were highly immunogenic; geometric means were 31 and 35 $\mu\text{g/mL}$ in the 7- to 11-month and 12- to 15-month age groups, respectively. Following two doses of *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine, both immunization protocols resulted in (1) equally high geometric mean antibody levels 1 month after immunization and (2) similar geometric mean antibody levels 6 months after immunization.

Conclusions.—*Haemophilus influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine induces antibody levels

that would be expected to protect infants from initial invasion and primes the immune system for an anamnestic response. Our data indicate that if a booster immunization is needed, *H influenzae* type b polysaccharide vaccine could be an alternative to *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine.

(AJDC. 1991;145:898-900)

The originally licensed *Haemophilus influenzae* type b (Hib) vaccine, *H influenzae* type b polysaccharide (HbPs) vaccine, is poorly immunogenic in children younger than 18 to 24 months and does not induce immunologic memory.¹⁻⁴ Vaccines that link the capsular saccharide of Hib to a protein (conjugate vaccines) have two goals. The primary goal is to stimulate an infant's immature immune system to produce anti-HbPs antibody levels that are high enough and last long enough to prevent invasive disease. The second is to prime the immune system so that exposure to Hib can rapidly stimulate clonal expansion of already-primed B cells. Two conjugate vaccines, *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate vaccine (HbOC) (HibTITER; Praxis Biologics Inc, Rochester, NY) and *Haemophilus* b Conjugate Vaccine (Meningococcal Protein Conjugate) (PedvaxHIB; Merck Sharp & Dohme Laboratories, West Point, Pa), are licensed for use beginning at 2 months of age.^{5,6} Our study documents the immunogenicity of various sequential combinations of HbOC and HbPs vaccines in infants aged 7 to 15 months of age and the ability of HbOC to prime these infants for a response to HbPs vaccine.

SUBJECTS AND METHODS

Subject Selection

Children aged between 7 and 15 months were eligible to participate if they had no serious chronic illness, no history of Hib disease, no previous immunization with either HbPs vaccine or a conjugate Hib vaccine, and no history or physical findings suggestive of an acute febrile illness. Children were enrolled in the study, approved by the Institutional Review Board of Grand View Hospital, Sellersville, Pa, after parental written informed consent was obtained.

Vaccines and Vaccine Administration

The HbPs vaccine (b-Capsa I, lot 038AL; Praxis Biologics Inc), containing 25 $\mu\text{g/mL}$ of capsular polysaccharide per 0.5 $\mu\text{g/mL}$, or the HbOC vaccine (HibTITER, lots BRH512 and A2K61), containing

Accepted for publication March 3, 1991.

From Pennridge Pediatrics Associates, Sellersville, Pa (Drs Rothstein, Schiller, Girone, Hipp, Souder, and Bernstein); St Christopher's Hospital for Children and Temple University School of Medicine, Philadelphia, Pa (Drs Rothstein, Schiller, Girone, Hipp, Souder, and Bernstein); and Praxis Biologics Inc, Rochester, NY (Drs Madore and Smith and Ms Johnson).

Reprint requests to 711 Lawn Ave, Sellersville, PA 18960 (Dr Rothstein).

Table 1.—Comparison of Anti-*Haemophilus influenzae* Type b Polysaccharide (HbPs) Antibody Responses of 7- to 11-Month-Old Infants According to Different Vaccination Protocols

Vaccination Schedule†	Months After First Vaccination	GM Anti-HbPs Antibody, µg/mL*					
		No.	HbOC/HbOC/HbOC	No.	HbOC/HbOC/HbPs	No.	HbOC/HbPs/HbPs
P/V	0	48	0.11 (0.08-0.15)	33	0.11 (0.08-0.17)	39	0.12 (0.08-0.17)
P/V	2	48	2.91 (0.64-13.30)	33	4.86 (1.74-13.58)	39	3.84 (0.91-16.25)
P	3	48	29.05 (12.35-68.35)	33	34.57 (25.49-46.88)	38	9.83‡ (2.58-37.51)
P/V	6	47	15.97 (5.50-46.41)	33	19.04 (8.47-42.83)	39	3.72‡ (0.98-14.17)
P	7	48	37.93 (32.32-44.52)	33	37.52 (32.06-43.91)	38	11.89‡ (2.91-48.59)
P	12	48	16.38 (7.82-34.33)	33	16.76 (7.80-36.02)	33	6.76‡ (2.22-20.62)

*GM indicates geometric mean; HbOC, *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate. Numbers in parentheses are SDs.

†P indicates phlebotomy; V, vaccination.

‡Significantly different from response in HbOC/HbOC/HbOC and HbOC/HbOC/HbPs groups ($P < .05$).

Table 2.—Comparison of Anti-*Haemophilus influenzae* Type b Polysaccharide (HbPs) Antibody Responses of 12- to 15-Month-Old Infants According to Different Vaccination Protocols

Vaccination Schedule	Months After First Vaccination	GM Anti-HbPs Antibody, µg/mL*					
		No.	HbOC/HbOC/HbOC	No.	HbOC/HbOC/HbPs	No.	HbOC/HbPs/HbPs
P/V	0	23	0.15 (0.09-0.26)	14	0.16 (0.09-0.29)	14	0.13 (0.10-0.16)
P/V	2	23	10.91 (3.24-36.71)	14	12.10 (4.70-31.81)	13	8.31 (2.65-26.04)
P	3	23	33.37 (21.78-51.14)	14	37.27 (28.62-48.54)	14	9.34‡ (1.62-53.86)
P/V	6	23	22.86 (12.50-41.81)	14	26.79 (16.24-44.20)	14	5.10‡ (1.38-18.82)
P	7	23	39.55 (38.07-41.10)	14	37.97 (31.23-46.15)	14	17.48‡ (5.00-61.05)
P	12	22	25.39 (13.96-46.18)	14	27.28 (16.99-43.18)	14	10.83‡ (2.57-45.65)

*GM indicates geometric mean; HbOC, *H influenzae* b oligosaccharide-CRM₁₉₇ conjugate. Numbers in parentheses are SDs.

†P indicates phlebotomy; V, vaccination.

‡Significantly different from response in HbOC/HbOC/HbOC and HbOC/HbOC/HbPs groups ($P < .05$).

10 µg/mL of capsular derived oligosaccharide and 25 µg/mL of CRM₁₉₇ per 0.5 µg/mL, was administered as a 0.5-mL intramuscular dose, as recommended by the manufacturer. A three-dose sequential schedule was used to immunize infants on study day 0 and at 2 and 6 months after initial immunization.

Study Design

Subjects were consecutively and alternately assigned to one of three immunization protocols. As shown in Tables 1 and 2, subjects were immunized with three doses of HbOC, two doses of HbOC followed by one dose of HbPs, or one dose of HbOC followed by two doses of HbPs. Further enrollment in the HbPs groups was terminated after it became apparent that the antibody response to HbPs in one of the groups was statistically significantly less than that to HbOC (Tables 1 and 2). Therefore, more infants were enrolled in the group that received three doses of HbOC than in the other two groups.

Specimen Collection

Venous blood was obtained before each immunization, 1 month after the second and third immunizations, and 6 months after the third immunization. Blood was separated within 4 hours of collection, and serum samples were frozen until they were analyzed for anti-HbPs antibodies.

Serologic Assays

All serum samples were coded so that Praxis Biologics Inc laboratory personnel were unaware of the subjects' protocol assignment. Total serum antibody to HbPs was quantitated by a Farr-type radioantigen binding assay, as previously described.⁷ The anti-HbPs antibody levels in each group were evaluated by determining the geometric mean (GM). Values at or below 0.10 µg/mL were recorded as 0.10 µg/mL and those equal to or greater than 40.00 µg/mL were recorded as 40.00 µg/mL. The

significance of differences in the GM between groups was determined by least square means analysis.

RESULTS

One hundred eighty-one white infants 7 to 15 months of age were enrolled. One hundred seventy-five infants (96.4%) completed the study. Four infants with initial anti-HbPs antibody levels of greater than 1 µg/mL were eliminated from further analysis. Of the remaining 171 infants, 82 were female and 89 were male. The sex distribution and mean ages of the immunization groups were similar within each age group. The mean age at the time of first immunization for each group was between 8.3 and 9.2 months and 13.1 and 13.3 months for the younger and older groups, respectively.

Analysis of Anti-HbPs Antibody Response

The immunologic response to each immunization protocol was evaluated in infants aged 7 to 11 months (Table 1) and 12 to 15 months (Table 2). Within each age group, the GM anti-HbPs antibody levels before and after one dose of HbOC vaccine were not statistically different. Older infants (12 to 15 months old) responded to one dose of HbOC with greater GM antibody levels than younger infants (7 to 11 months old). Eighty-five percent of 7- to 11-month-old and 98% of 12- to 15-month-old infants had anti-HbPs antibody values greater than 1 µg/mL after a single dose of HbOC.

Following a second dose of HbOC, the GM anti-HbPs antibody of the 7- to 11-month-old infants rose sevenfold to 10-fold further (Table 1). In the older group, the second dose of HbOC increased the GM threefold further (Table 2). Irrespective of the age of the infant at the time of the initial immunization, the GM anti-HbPs antibody level was high (29 to 37

μg/mL) following two doses of HbOC. Two doses of HbOC resulted in a greater than 200-fold increase in GM anti-HbPs antibodies over the preimmunization levels. Ninety-nine percent of the infants had anti-HbPs levels greater than 1 μg/L. Ninety-six percent had levels greater than 10 μg/mL.

In contrast, infants who were immunized with one dose of HbOC followed by HbPs 2 months later showed a 72- to 82-fold increase over the preimmunization antibody level. This increase was seen irrespective of age at initial immunization. The GM anti-HbPs antibody levels were 9.83 μg/mL (92% ≥ 1 μg/mL) and 9.34 μg/mL (86% ≥ 1 μg/mL) in the younger and older groups, respectively.

Further evaluation of the individual responses in the younger age group indicates that 21 of the 39 individuals given HbPs 2 months after an initial dose of HbOC showed a greater than twofold increase in GM anti-HbPs antibody. The GM of these 21 responders rose from 2.41 to 17.01 μg/mL (SD, 7.2 to 40.2 μg/mL) after the HbPs immunization. The mean age of this 7- to 11-month-old responder subgroup was 10.6 months (range, 9 to 13 months) at the time of their HbPs immunization. In contrast, the pre- and post-HbPs immunization GM antibody level in the nonresponders (those having less than twofold antibody rise) was 5.94 and 4.75 μg/mL, respectively. These two groups (responders and nonresponders) were not distinguishable by preimmunization anti-HbPs levels (nonresponder GM, 0.11) or by age (nonresponder mean age, 10.8 months; range, 9 to 13 months). When these nonresponders to HbPs received a second dose of HbPs 4 months later, 13 of the 17 showed a greater than twofold increase (one child's specimen was unavailable). At the time of their third immunization (one dose of HbOC followed by two doses of HbPs), the ages of the four remaining nonresponders were 13.2, 13.6, 14.8, and 15.5 months.

Two primary doses of HbOC resulted in high-GM anti-HbPs antibody levels, approaching the upper limit of data analysis (40.0 μg/mL) in both age groups. In those in whom antibody levels declined after the second dose of HbOC, a third dose of either HbOC or HbPs boosted the anti-HbPs antibodies back to levels that approached the upper limit of the assay.

Irrespective of the immunization schedule or the age at the time of initial examination, high anti-HbPs antibody levels were sustained over time. Six months following the third immunization, when children were 19 to 27 months of age, all who were in the groups that received three doses of HbOC or two doses of HbOC followed by one dose of HbPs had antibody levels greater than 1 μg/mL. Of those who received one dose of HbOC followed by two doses of HbPs, 93% had levels greater than 1 μg/mL, irrespective of age group.

COMMENT

To our knowledge, ours is the first study to use HbPs in a primary immunization series following an initial dose with an Hib conjugate vaccine in infants younger than 15 months. Our observations show that, following a single dose of HbOC, (1) HbPs can boost anti-HbPs antibody levels in infants who, because of age, would not be expected to respond with this frequency or to this level; (2) HbPs boosts anti-HbPs antibody to the same GM antibody level in infants who received their primary dose of HbOC whether they were 7 to 11 or 12 to 15 months of age; (3) a second vaccination with HbOC results in a greater GM anti-HbPs antibody level than when the second vaccination is HbPs; and (4) when given after two doses of HbOC, both HbPs and HbOC boost GM antibody levels to the same high value, the values decline to the same levels

6 months after immunization, and in all the children levels were maintained that have been correlated with long-term immunity after immunization with an HbPs vaccine (≥ 1 μg/mL).⁸

The greater response when the second dose is HbOC rather than HbPs may reflect recruitment of new clones of B cells (T-cell dependent) along with better stimulation of already-primed B cells. The HbPs, as a second dose in these young infants, probably only stimulates already-primed B cells. It appears that some children may not be primed within 2 months after a single dose of HbOC, as evidenced by their lack of response to HbPs. However, almost all of these children responded to a second dose of HbPs administered 4 months later, and all had anti-HbPs antibody concentrations of greater than 1 μg/mL when evaluated 6 months after their last immunization. The response to the second dose of HbPs may be related to both age and prior immunization.

While current recommendations for immunization of infants 7 to 11 months of age include a booster, the data from this study indicate that two doses of HbOC stimulate high antibody levels. There may not be an advantage to vaccinating this age group with three doses of HbOC. If three doses are desirable, HbPs could be a reasonable alternative following two doses of HbOC.

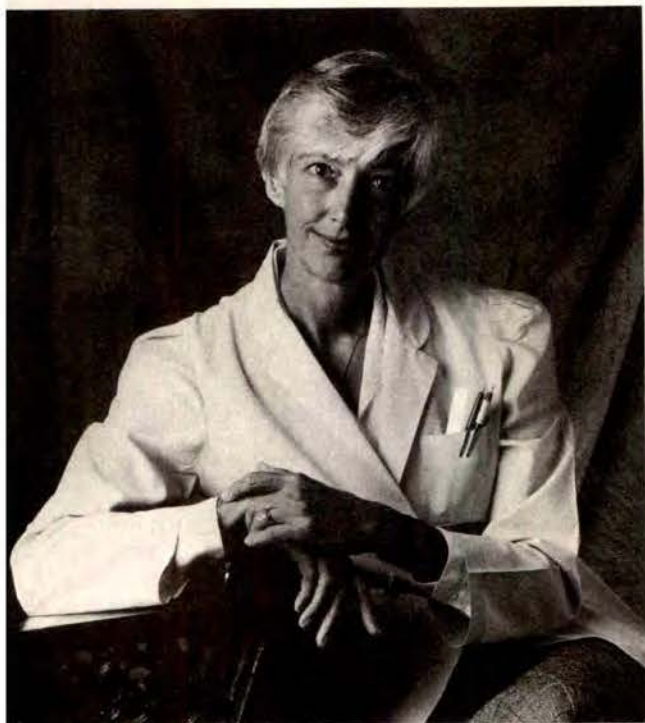
The more important implication of these data is that in the months after successful primary immunization, as the expected decline in antibody levels occurs, exposure to the polysaccharide (probably representative of the organism) should elicit an accelerated memory response that will aid in protection against invasive *Haemophilus* disease and help to maintain immunity. The HbOC not only generates high levels of anti-HbPs antibodies following one or two doses, but it appears to prime, as evidenced by a further antibody rise when HbPs vaccine is administered 2 to 4 months later.

The helpful review by Sarah S. Long, MD, is thoroughly appreciated. We acknowledge the superb support of Dorothy Kratz, RN, and Jean Bitner, RN, as well as the rest of the staff of Pennridge Pediatrics Associates, Sellersville, Pa. The dedication of the staff of the Immunobiologic Service Department and the Clinical Studies Department at Praxis Biologics Inc, especially Donna Phipps, MS, Carolyn Cimino, and Kim Kukfa, MS, are also deeply appreciated.

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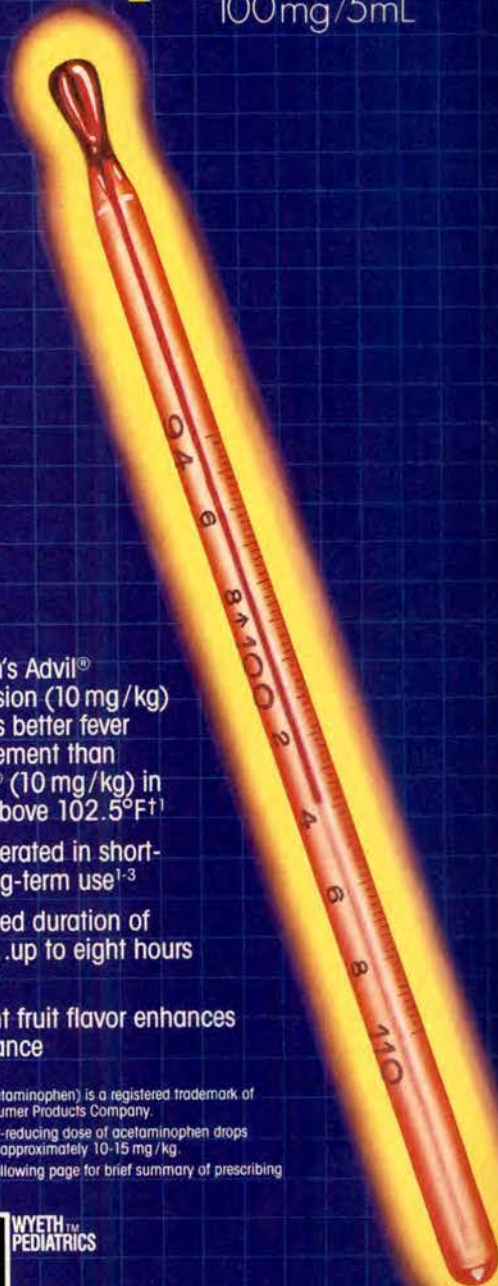
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INDICATIONS: CHILDREN'S ADVIL® SUSPENSION is indicated for the reduction of fever in patients aged 12 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

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CONTRAINDICATIONS: Patients hypersensitive to ibuprofen or patients with all or part of the syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions to ibuprofen have occurred in such patients.

WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aseptic meningitis with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of ibuprofen. CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: Coumarin-type Anticoagulants: Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H₂ Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 1% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain, fullness of the GI tract (bloating and flatulence), heartburn, indigestion, nausea, and vomiting; dizziness; headache, nervousness, pruritus, rash* (including maculopapular type); tinnitus; decreased appetite; edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis, alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions, aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss, agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura; congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations, anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting, acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria, dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri, photallergic skin reactions, toxic epidermal necrolysis, cataracts, conjunctivitis, diplopia, optic neuritis, bleeding episodes (e.g., epistaxis, menorrhagia), acidosis, gynecomastia, hypoglycemic reactions, arthralgias (sinus tachycardia, sinus bradycardia), angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness, renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles.

Caution: Federal law prohibits dispensing without prescription.

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References: 1. Sandler RB, et al: *Am J Clin Nutr* 1985;42:270-274. 2. Rubin K: *Pediatric By-Line* 1985;4(3):1, 4-6. 3. Marston R, Raper N: *National Food Review* 1987;36:18-23. 4. Heaney RH: *The Physician and Sportsmedicine* 1987;15:83-88.



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Transfusion Therapy in Neonates

Ronald G. Strauss, MD

• Infants, particularly those who were very small premature neonates, are among the most common of all patient groups to undergo extensive transfusion. It is estimated that approximately 300 000 neonates undergo transfusions annually. Most infants who undergo transfusion are exposed to multiple blood donors, and although each exposure poses only a small risk, the potential for adverse effects of multiple transfusions is not trivial. Transfusion practices for neonates are controversial, variable, and based on scanty scientific information. For the most part, controlled scientific studies have not been performed to clearly establish the indications for the transfusion of blood components to neonates. Considering these limitations, guidelines are offered for the transfusion of red blood cells, platelets, and neutrophils into neonates.

(AJDC. 1991;145:904-911)

Some neonates require multiple blood transfusions, and the risks of transfusion, although infrequent, are not trivial. Thus, knowledge of neonatal transfusion medicine is crucial for optimal pediatric practice.

THE NEED FOR MULTIPLE TRANSFUSIONS

Infants, particularly those who were very small premature neonates, are among the most common of all patient groups to undergo extensive transfusions. Of the 38 000 premature neonates with birth weights (BW) of less than 1500 g estimated to be born annually in the United States,^{1,2} 80% will require multiple red blood cell (RBC) transfusions—many infants will receive cumulative transfusion volumes exceeding their total blood volumes.^{3,4} Based on a review of eight studies, Sacher et al⁴ concluded that infants undergoing multiple transfusions typically are exposed to eight to 10 different donors (range, two to 18 donors). Likewise, results of a study conducted at our institution between 1983 and 1984⁵ showed a substantial use of RBC transfusions from multiple donors: 53 infants received 683 RBC transfusions from 503 different donors (mean number of donors per neonate, 9.5). In an unpublished study (R.G.S., unpublished data, 1989) performed

between 1988 and 1989 to assess current practices, a similar rate was documented: 38 (78%) of 49 infants with BWs of less than 1500 g received an average of 10 RBC transfusions per infant, with a mean exposure to slightly more than six donors per neonate (Table 1). In addition, about 16% of infants underwent transfusions of other blood components. Thus, concerns about transfusion-associated diseases have not caused a major reduction in blood transfusions by neonatologists—presumably because RBC transfusions are perceived to be mandatory for the optimal care of sick premature infants.

Assuming my data (Table 1) and that of others^{3,4,6} are representative of current national practices, approximately 29 640 low-BW infants will receive 296 400 RBC transfusions annually. Importantly, the long-term survival of infants with BWs of less than 1500 g continues to improve, which results in an increasing number of infants requiring multiple RBC transfusions. In addition, occasional transfusions are given to infants with BWs of greater than 1500 g. It is very alarming that, by current practices, many infants will be exposed to different donors for most transfusions. Thus, the importance of sound knowledge about neonatal transfusion practices is emphasized by the mandatory and crucial role of blood component transfusions in the treatment of extremely small, premature neonates.

THE RISK OF TRANSFUSIONS

It is logical to conclude that exposure to multiple blood donors will increase the potential for adverse effects, particularly transfusion-associated infections. The rate of transfusion-associated infections, although not always directly proportional to the frequency of donor exposure, increases when multiple transfusions are given.^{7,8} To eliminate the transmission of infections from donors, blood banks continuously improve medical screening of blood donors and laboratory testing of donated blood. For every donation, donors are advised that they are not to donate if they are in high-risk groups (eg, intravenous drug abusers). Donors are directly questioned about high-risk behavior, and they must give written confirmation that they are not involved in such behavior. A complete medical history is recorded and, if needed, a physical examination is conducted. Laboratory testing is performed to detect hepatitis, syphilis, and retrovirus (human immunodeficiency virus [HIV] type 1 and human T-cell leukemia/lymphoma virus type I or II) infections. However, to ensure maximum safety, these measures employed to

Accepted for publication April 1, 1991.

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Table 1.—RBC Transfusions in Preterm Infants at the University of Iowa—1988-1989*

Clinical Characteristics of Infants	Data
All Infants Reviewed (n=49)	
No. (%) who underwent RBC transfusions	38 (78)
No. (%) who underwent transfusions of other components	8 (16)
Infants Who Underwent Transfusion (n=38)	
No. of RBC transfusions (mean \pm SD)	10.0 \pm 8.3
No. of RBC donors (mean \pm SD)	6.2 \pm 5.3
No. (%) who underwent >4 RBC transfusions	31 (82)
No. (%) who underwent >15 RBC transfusions	10 (26)
Maximum No. of RBC transfusions undergone	40

*RBC indicates red blood cell. All infants weighed less than 1500 g at birth.

improve transfusion safety must be coupled with efforts to diminish the need for homologous transfusions.

The percentage of infants and children who acquire HIV via transfusion is disproportionately high compared with the number of adults thus infected. In one survey⁹ excluding hemophiliacs, 15% of childhood cases of HIV infection were due to blood transfusions compared with 2% of adulthood cases of HIV infection.⁹ These rates were determined before current methods of donor screening and testing were used, and, thus, are overestimates of the current rate of transfusion-associated HIV infection. However, the data illustrate the importance of transfusions as a route for transmitting blood-borne organisms to neonates. The current risk of an infected donor not being detected with testing is estimated to be about one in 1 million.¹⁰ Because the exact figure is unknown, some controversy exists, and most experts accept a rate of between one and 20 per million.

The current rate of transfusion-associated hepatitis has not been determined accurately in infants. Although the incidence of non-A, non-B hepatitis (which, in most cases, is presumed to be due to the hepatitis C virus) is believed to be low,¹¹ the rate is difficult to establish because, until very recently, the diagnosis was made by documenting an unexplained elevation in serum alanine aminotransferase occurring within 6 months of transfusion. Long-term serial measurements of alanine aminotransferase during the perinatal period have been rarely reported, and alanine aminotransferase values are higher and more variable in infants who apparently are healthy than are values in subjects of other ages.¹² Nonetheless, non-A, non-B hepatitis is of concern because it is the most common transfusion-related viral infection and has the potential for long-term toxic effects.¹³ Disorders leading to long-term morbidity (eg, posthepatic cirrhosis and hepatic cancer) are particularly alarming when they occur during infancy because of the potential for an extended disability requiring costly care.

The importance of transfusion-associated cytomegalovirus (CMV) infection in neonates is controversial. Studies conducted during the 1970s and early 1980s reported a disturbingly high incidence (25% to 50%) of CMV infection in neonates who had undergone transfusion.¹⁴ This was particularly true in those who underwent the most extensive transfusions, some of whom died. Several recent studies indicate a diminishing, almost negligible risk.¹⁴

However, these studies have been criticized,¹⁵ and the importance of transfusion-associated CMV infection and the need for special precautions (use of CMV-seronegative donors or components markedly depleted of leukocytes) when conducting transfusions in neonates remains controversial. The American Association of Blood Banks, in its *Standards for Blood Banks and Transfusion Services*,¹⁶ has recommended that cellular blood products with low risks of transmitting CMV infection be given to infants with BWs of less than 1200 g who are seronegative for antibody to CMV or of unknown serostatus if they are being managed in hospitals in which CMV is known to be a problem. The transmission of CMV to infants has implications beyond immediate infant morbidity and mortality. Infected infants can transmit CMV to their mothers and to other susceptible contacts.

Other transfusion-associated conditions of noninfectious nature that may occur in infants include fluid overload, graft-vs-host disease,^{17,18} electrolyte and acid-base imbalances, iron overload,¹⁹ increased susceptibility to oxidant damage,²⁰ exposure to plasticizers,²¹ hemolysis when T-antigen activation of RBCs has occurred,²² immunosuppression,²³ and alloimmunization,¹¹ although, in limited studies,⁵ alloimmunization to RBC and leukocyte antigens has been shown to be uncommon in infants. Regarding graft-vs-host disease and techniques for irradiation, the American Association of Blood Banks¹⁶ recommends that cellular blood products be irradiated with a minimum of 15 Gy to prevent graft-vs-host disease in fetuses (intrauterine transfusion), in selected immunocompromised recipients, and in patients receiving transfusion products from first-degree relatives. In practice, "selected immunocompromised recipients" are usually defined as bone marrow transplant recipients, patients with congenital defects of cell-mediated immunity, and patients with disseminated reticuloendothelial cancer undergoing therapy. Although enthusiasm for the transfusion of irradiated blood components is variable, it is difficult to justify scientifically the exclusive use of these products in neonates in general, even if they are premature or infected with HIV. Some adverse effects occur only with massive transfusions, such as exchange transfusions, and are rare in the usual, small-volume RBC transfusion. The relationship of some alleged adverse effects to transfusions is controversial.²⁴ Nonetheless, the risks of transfusion are significant, and blood components should be transfused only when necessary.

INDICATIONS FOR NEONATAL TRANSFUSION

The lack of a rational approach to transfusion practices^{4,25,26} stems from limited knowledge of the cellular and molecular biology of hematopoiesis during the perinatal period as well as from a lack of understanding of the infant's response to severe cytopenia. Data from clinical studies of infants are sparse and difficult to interpret because of the precarious and heterogeneous medical condition of these patients. Even the deceptively simple task of obtaining sufficient blood to conduct definitive studies is a major impediment because of small total blood volumes and difficult vascular access. Although, in some instances, the value of transfusions is clear (eg, transfusing RBCs to treat anemia that has caused congestive heart failure and transfusing platelets to treat severe thrombocytopenia with bleeding), in others, it is not. Following are reasonable guidelines for the transfusion of the three most

frequently used cellular components—RBCs, platelets, and neutrophils (granulocytes).

RBC Transfusions

Generally, RBC transfusion is performed to maintain a level of hematocrit believed to be most desirable for each neonate's clinical status.²⁷ It is widely recognized that this clinical approach is imprecise, and consideration of more physiologic indications such as RBC mass, available oxygen, and measurements of oxygen delivery and tissue extraction has been suggested. However, the means by which these techniques can best be applied to everyday practice are undefined. Clearly established indications for neonatal RBC transfusions, based on controlled scientific studies, do not exist. In many clinical situations, the need for RBC transfusion seems logical, but often efficacy has not been established, and a complete understanding of the risks is lacking. Because of the limited data available, it is important that pediatricians critically evaluate the following recommendations in light of neonatal practice at their institutions. Most RBC transfusions performed in neonates are of small volume (5 to 15 mL of RBCs per kilogram of body weight) and are repeated frequently.²⁷ The usual indications for small-volume transfusions are discussed separately.

Replacement of Blood Drawn for Laboratory Studies.—This indication accounts for about 90% of all RBC transfusions in neonates.²⁸ Although laboratory micro methods can be used, cumulative blood losses due to laboratory sampling are proportionately very large.⁴ Attempts are being made to limit blood sampling via the use of indwelling catheters with specific transducers, transcutaneous electrodes, and monitors. Until these are available for routine use, the practice of replacing drawn blood with transfused RBCs will continue.²⁹ Often, RBCs are replaced when 5% of the estimated total blood volume has been removed from neonates requiring frequent monitoring. Replacement is frequently performed if the hematocrit has decreased rapidly and/or if mechanical ventilation is required. Some physicians do not replace RBCs until about 10% of the blood volume has been drawn if the neonate is relatively stable and the hematocrit level reasonable.

Maintenance of Hematocrit Levels of Greater Than 0.40 During Severe Respiratory Disease.—In neonates with severe respiratory disease, particularly those requiring oxygen and/or ventilator support, it is customary to maintain the hematocrit level at greater than 0.40 (blood hemoglobin, >130 g/L). Proponents believe that transfused RBCs containing adult hemoglobin are most likely to provide satisfactory oxygen delivery throughout the period of diminished pulmonary function. Although this practice is widely recommended, little evidence is available to establish its efficacy, define its optimal use (ie, the best hematocrit level during each clinical situation), or document its risks.²⁵ A recent study³⁰ of 10 infants with severe (oxygen-dependent) bronchopulmonary dysplasia demonstrated improvement of physiologic end points (increased systemic oxygen transport and decreased oxygen use) after small-volume RBC transfusions. It is notable that the blood hemoglobin levels alone did not predict which infants would benefit from transfusion.³⁰ More information is needed to define the precise indications for and benefits of RBC transfusions as based on measurements of tissue oxygenation rather than on hematocrit levels alone.

Maintenance of Hematocrit Levels of Greater Than 0.40 in Neonates With Symptomatic Heart Disease.—Consistent with the rationale for optimal oxygen delivery discussed above, it seems logical to maintain hematocrit levels of greater than 0.40 in neonates with severe congenital heart disease leading to either cyanosis or congestive heart failure. Regarding the latter, isovolumic exchange transfusions were used to treat nine infants with ventricular septal defects and large left-to-right shunts.³¹ The postpartum decreases in hematocrit levels had produced decreases in blood viscosity that resulted in decreased pulmonary vascular resistance and increased left-to-right shunting. Exchange transfusion increased the mean blood hemoglobin level from 99 to 146 g/L—a change that increased pulmonary vascular resistance and decreased both left-to-right shunting and pulmonary blood flow. These changes lowered heart rate and left ventricular stroke volume without compromising oxygen transport to the tissues. Extending these observations to neonatal patients with patent ductus arteriosus, Rosenthal³² suggested that RBC transfusions might increase pulmonary vascular resistance, enhance ductal closure, and alleviate high-output cardiac failure. This indication seems tenuous. Because transfusions may transiently increase blood volume and exacerbate cardiac failure, the precise role of RBC transfusions in the treatment of severe patent ductus arteriosus requires more study.

Maintenance of Hematocrit Levels of Greater Than 0.30 in Neonates With Cardiopulmonary Problems.—Neonates who are relatively stable do not require RBC transfusions unless they exhibit clinical problems that are presumed to be related to the degree of anemia present. Proponents of transfusion therapy believe that anemia contributes to tachypnea, dyspnea, apnea, tachycardia, bradycardia, feeding difficulties, and lethargy and that these problems can be alleviated with RBC transfusions. Tachypnea, dyspnea, and apnea could be exacerbated by anemia as a consequence of decreased oxygen delivery to the respiratory center of the brain.³³ Generally, by the time healthy, premature infants reach the physiologic nadir of hemoglobin concentration, the respiratory center has become more mature and less sensitive to hypoxemia so that apnea is no longer a major problem. However, sick, premature infants become anemic earlier, and when anemia and severe apnea occur together it is tempting to believe that transfusion of RBCs might decrease the frequency of apneic episodes via an improvement in oxygen delivery to the central nervous system. Confirming the validity of this practice, RBC transfusions were shown to diminish irregular breathing patterns and episodes of bradycardia in anemic preterm infants when their mean hematocrit levels were increased from 27% to 36%.³⁴ However, beneficial effects of RBC transfusions on breathing patterns have not been found by all investigators.³⁵

Maintenance of Hematocrit Levels of Greater Than 0.30 in Neonates With Growth Failure.—Some neonatologists consider poor weight gain to be an indication for RBC transfusion, particularly if the hemoglobin concentration is below 100 g/L (hematocrit level, less than 0.30) and other signs of distress (eg, tachycardia, respiratory difficulty, weak suck, less vigorous cry, and less activity) are evident. The validity of this practice was confirmed by studies of infants with bronchopulmonary dysplasia in whom growth failure was ascribed to increased metabolic expenditure.³⁶ Stockman and Clark³⁷ investigated the effects of

RBC transfusion on weight gain in relatively stable, low-BW infants. Thirteen infants with BWs of less than 1500 g were studied for 1 week before and after transfusion. The mean (\pm SD) hemoglobin concentration increased from 85 ± 16 to 114 ± 21 g/L by transfusion, and mean daily weight gain increased from 20.8 ± 4.6 to 28.0 ± 6.3 g. Infants with the lowest hemoglobin values before transfusion exhibited the greatest increase in weight. Increased weight gain was associated with decreased metabolic rates (measured by oxygen consumption). The authors considered anemia as only one of several possible causes of growth failure, and they recommended RBC transfusions for treatment of growth failure in infants with low-normal or subnormal hemoglobin levels, providing nothing else could explain the poor weight gain.³⁷

Blank et al.³⁸ found no advantage for the prophylactic use of small-volume RBC transfusions in otherwise well, growing, premature infants. Fifty-six premature infants were randomly assigned to either a mandatory (prophylactic) transfusion group (hemoglobin maintained at greater than 100 g/L) or an elective (nontransfusion) group in which RBC transfusions were permitted only for treatment of marked clinical manifestations of anemia. Only four (13%) of 30 infants in the latter group underwent transfusion electively (once each for treatment of apnea). Characteristics of all patients at birth were similar to those of fetuses at about 30 weeks' gestation, and mean BWs were 1196 ± 279 g and 1145 ± 251 g for mandatory and elective transfusion groups, respectively. At discharge, the infants in the elective transfusion group exhibited significantly greater anemia and reticulocyte counts than did those receiving mandatory transfusions ($P < .01$; mean hemoglobin level, 91.0 ± 16.7 vs 117.5 ± 17.2 g/L; and mean reticulocyte count, $6\% \pm 3\%$ vs $3\% \pm 2\%$). Despite these differences, both groups were comparable in the number of days required to regain BW, discharge weight, length and cost of hospitalization, and frequency and severity of clinical problems. Thus, this study did not indicate benefits of mandatory, small-volume RBC transfusions to maintain hematocrit levels of greater than 0.30 in stable, growing, premature infants who were otherwise healthy.³⁸

In a similar study, Ross et al.³⁹ randomly assigned 16 preterm, clinically stable infants aged older than 1 month to either an RBC transfusion or a nontransfusion group. Infants with hematocrit levels of less than 0.29 were studied for 3 days before and after receiving either 10 mL of packed RBCs per kilogram of body weight or no transfusions for signs of improvement, as indicated by measures of cardiopulmonary function. Factors that identified infants most likely to benefit from RBC transfusions included pretransfusion heart rates of more than 152 beats per minute, presence of apnea/bradycardia requiring intervention, and elevated blood lactate levels.³⁹ Additional studies of this nature may help identify infants for whom RBC transfusions are indicated.

RBC Product for Transfusion.—The RBC product of choice for small-volume neonatal transfusions is sedimented RBC concentrate. Fresh units of whole blood are centrifuged, plasma is removed, storage additives are added as needed, and the RBC units are stored in an inverted position so that RBC concentrates with hematocrit levels approximately equal to 0.80 can be issued for transfusion. Most RBCs are infused at a dose of 5 to 15 mL/kg of body weight over 3 to 6 hours. Because of the small

Table 2.—Quantity of Additives in 10 mL of RBC Storage Solution*

Additive	Standard RBCs	Sedimented RBC Concentrate	Total Dose, mg/kg/h [†]	Estimated Toxic Dose
Glucose	86.0	86.0	17.20	240 mg/kg/h
Phosphate	1.3	1.3	0.26	60 mg/kg/d
Adenine	0.7	0.7	0.14	15 mg/kg/dose
Sodium	28.0	14.0	2.80	137 mg/kg/d
Citrate	6.5	3.3	0.66	180 mg/kg/h
Mannitol	22.0	11.0	2.20	360 mg/kg/d

*Data are from Luban et al.⁴⁰ RBC indicates red blood cell. Standard RBCs had hematocrit levels of 0.60, and sedimented RBC concentrate had a hematocrit level of 0.80. Values of additives in columns 2 and 3 are in milligrams. Sodium, citrate, and mannitol are confined to the extracellular fluid. Thus, the quantity infused decreases as the hematocrit level increases at the expense of a decreased extracellular fluid volume. In contrast, glucose, phosphate, and adenine are distributed throughout RBCs and the extracellular fluid and remain constant as long as the total volume infused is constant.

[†]Values are for 10 mL of sedimented RBC concentrate per kilogram of body weight infused over 5 hours.

quantity of extracellular fluid infused (hematocrit level, ≈ 0.80) and the slow rate of transfusion, the type of storage medium selected is not believed to pose risks to most premature infants.⁴⁰ Based on data calculated using RBCs stored in a chemical solution (Adsol; Fenwal Laboratories, Roundlake, Ill),⁴⁰ Table 2 shows the doses of additives infused with small-volume transfusions.

As an additional consideration, the traditional use of relatively fresh RBCs (less than 7 days of storage) is being challenged in hopes that donor exposure can be diminished by using a single unit of RBCs for each infant, regardless of the duration of RBC storage.²⁷ Neonatologists who object to this insist on transfusing fresh RBCs generally raise two objections: the increase in plasma potassium (K^+) levels and the decrease in RBC 2,3-diphosphoglycerate levels during extended storage. After 42 days of storage, plasma K^+ levels are approximately 50 mmol/L, a value that, at first glance, seems alarmingly high. With simple calculations, however, the dose of bioavailable plasma K^+ transfused is shown to be quite small. An infant weighing 1 kg undergoing a 10-mL/kg of body weight transfusion of packed RBCs (hematocrit level, ≈ 0.80) will receive 2 mL of plasma, or only 0.1 mmol/L of K^+ , via slow infusion. This dose is quite small compared with the usual daily K^+ requirement of 2 to 3 mmol/L per kilogram of body weight. As for the second objection, 2,3-diphosphoglycerate is totally depleted from RBCs by the 21st day of storage, and this is reflected in a p50 value that decreases from about 27 mm of Hg in fresh blood to 18 mm of Hg at outdate. The last value corresponds to the p50 in RBCs obtained from the blood of many normal premature infants at birth. Thus, the p50 of older transfused RBCs is comparable with that of RBCs produced by the infant's own bone marrow. Moreover, these older RBCs provide an advantage because the p50 of transfused RBCs (but not endogenous cells) increases rapidly after transfusion as 2,3-diphosphoglycerate regenerates within hours. Thus, small-volume transfusions with older RBCs appear to pose no substantive risks to relatively stable, premature infants, and their acceptance as a suitable blood component likely will diminish donor exposure.

Platelet Transfusions

To my knowledge, no controlled clinical trials have been reported in the literature to establish the efficacy of platelet transfusions in high-risk, thrombocytopenic infants. Based on general knowledge of the risks of thrombocytopenia and the success of platelet transfusions,⁴¹ it seems logical for thrombocytopenic infants to undergo platelet transfusions.⁴² A major indication for platelet transfusion during the perinatal period is hemorrhage in infants with blood platelet counts of less than $50 \times 10^9/L$. Platelet transfusions are also sometimes recommended for infants to treat bleeding that occurs with higher platelet counts (between $50 \times 10^9/L$ and $100 \times 10^9/L$), to diminish risk of intracranial hemorrhage in high-risk premature infants with platelet counts of less than $100 \times 10^9/L$, or to prevent bleeding when platelet levels are below a predetermined value—usually between $20 \times 10^9/L$ and $100 \times 10^9/L$, depending on the status of the infant being treated (prophylactic platelet transfusion).

Although the underlying cause of thrombocytopenia must be identified and treated, it seems logical, for several reasons, for neonates to undergo platelet transfusion when the blood platelet count is less than $20 \times 10^9/L$, regardless of whether overt bleeding is present. One reason is that this severity of thrombocytopenia is the level at which other patients are known to be at greatest risk of experiencing spontaneous hemorrhage.⁴¹ Another reason is that even healthy neonates exhibit hemostatic abnormalities of both platelets and clotting proteins. Almost any type of stress can accentuate these abnormalities and/or precipitate thrombocytopenia. Neonatal platelet dysfunction and the other abnormalities of hemostasis at this age might increase the potential for actual hemorrhage beyond that expected for the severity of thrombocytopenia.⁴³ A third reason is that severe thrombocytopenia occurs most often in sick infants who are receiving medications that may compromise platelet function; platelet transfusion may reverse some of these adverse effects. Because all of these factors are accentuated in low-BW infants, some neonatologists prefer platelet transfusion when the platelet count is less than $50 \times 10^9/L$ in stable premature neonates or less than $100 \times 10^9/L$ in sick, premature neonates.⁴⁴ Intracranial hemorrhage occurs frequently during the neonatal period in sick, low-BW neonates, and although the etiologic role of thrombocytopenia and the therapeutic benefit of platelet transfusion have not been conclusively established in this disorder, it seems logical to treat severe thrombocytopenia when it occurs in high-risk infants.^{44,45}

The goal of most platelet transfusions is to increase the platelet count to greater than $100 \times 10^9/L$. This can be achieved, consistently, with the infusion of 10 mL of standard platelet concentrates per kilogram of BW. These concentrates are obtained either via centrifugation of fresh units of whole blood or via automated plateletpheresis.⁴² These procedures are based on the following assumptions and calculations.

1. A 50-mL platelet concentrate from whole blood contains approximately 5×10^{10} platelets. If a 300-mL apheresis platelet unit contains approximately 3×10^{11} platelets, 50 mL will contain 5×10^{10} platelets. Thus, 10 mL of most platelet concentrates will contain approximately 1×10^{10} platelets.

2. The total blood volume of a 1-kg neonate is between 80 and 100 mL. For ease of calculations, 100 mL is assumed

as the blood volume into which the platelet concentrate will be infused. With a hematocrit level of 0.50, the plasma volume will be 0.05 L.

3. An infusion of 10 mL of platelet concentrate (10×10^9 platelets) into a 1-kg neonate with a 0.1-L blood volume will increase the blood platelet count by $100 \times 10^9/L$. Using the plasma volume as the volume of distribution, the platelet count would increase about $200 \times 10^9/L$. Because recovery in the bloodstream is always less than 100% of the dose infused, the yield of platelets in the concentrate is variable, and turnover is often accelerated, a postinfusion platelet count should always be obtained to determine whether additional platelet transfusions are needed.

Platelet concentrates should be transfused as rapidly as the neonate's overall condition permits, certainly within 2 hours. Generally, 10 mL/kg of BW is not an excessive volume—providing intakes of other intravenous fluids, medications, and nutrients are monitored and adjusted as needed. Although proven methods exist to reduce the volume of platelet concentrates,^{46,47} additional processing should be performed with great care because of possible platelet loss, clumping, and dysfunction caused by the additional handling. Platelet concentrates contain viable lymphocytes, and, like all cellular blood products, they should be considered for irradiation to prevent graft-vs-host disease, especially when the donor and neonate recipient are first-degree relatives.

Granulocyte (Neutrophil) Transfusions

Neonates are susceptible to severe bacterial infections, and several defects of neonatal body defenses have been reported as possible contributing factors. Abnormalities of neonatal neutrophils (polymorphonuclear neutrophil leukocytes [PMNs]) include absolute and relative neutropenia, diminished chemotaxis, abnormal adhesion and aggregation, defective cellular orientation and receptor capping, decreased deformability, inability to alter membrane potential during stimulation, imbalances of oxidative metabolism, and diminished ability to withstand oxidant stress.⁴⁸ The age at which neonatal PMN defects disappear, and whether the change is abrupt or gradual, are unknown.

Neutropenia can occur during neonatal bacterial infections, particularly with fulminant sepsis. When contrasted with the neutrophilia of normal neonates, it is considered abnormal for the absolute blood PMN count to be less than $3 \times 10^9/L$ during the first week of life. Although an abnormally low PMN count can occur in neonates with disorders as diverse as sepsis, asphyxia, and maternal hypertension, suspicion of severe bacterial infection must always be high when relative neutropenia (neutrophil count, less than $3 \times 10^9/L$) occurs. The mechanisms responsible are only partially known, but abnormalities of neonatal granulopoiesis frequently are involved. Committed precursors to PMN development are fewer in neonatal marrow than in the marrow of older subjects, and they proliferate at a rate close to capacity even when studied during an apparently basal state. Thus, neonatal marrow is unable to rapidly increase and sustain PMN output in response to an infection.

Granulocyte transfusions have been used to treat infections in patients of all ages exhibiting either neutropenia or PMN dysfunction. Thus, a rationale exists for combining granulocyte transfusions with antibiotics to treat septic neonates—subjects in whom both neutropenia and PMN

dysfunction have been demonstrated. This topic was recently reviewed,⁴⁹ and only information particularly germane to the transfusion medicine aspects of this topic are discussed herein.

Granulocyte transfusions have been used to treat neonatal sepsis regardless of whether neutropenia is present. Neonates exhibiting fulminant sepsis, relative neutropenia (less than 3×10^9 PMNs per liter of blood during the first week of life), and severely diminished PMN marrow storage pools (less than 10% of nucleated marrow cells being postmitotic PMNs) are at particularly high risk of dying if treated only with antibiotics. Eleven publications⁵⁰⁻⁶⁰ report the use of granulocyte transfusion to treat infected neonates. Six were designed as controlled studies.^{50-53,58,59} That four of these six studies found granulocyte transfusion to be significantly beneficial is encouraging.³⁰⁻⁵³ Although five of the six controlled studies incorporated randomized trials, two included subjects who did not undergo transfusion and who were deemed ineligible for randomization.^{50,59} One study is described in two reports. It was reported first as a somewhat preliminary trial⁵² and again after expansion and slight modification.⁵³ Although the controlled studies contained obvious flaws, they had important features.

Laurenti et al⁵¹ studied mostly premature neonates, many of whom were infected with an antibiotic-resistant *Klebsiella* bacteria. Neutropenia was not a criterion for entry. Neonates received two to 15 daily transfusions of granulocytes prepared via filtration leukapheresis at a dose of 0.5×10^9 to 1.0×10^9 per kilogram of body weight and fared strikingly better (90% survival rate) than did those receiving only antibiotics (28% survival rate). One lesson of this study is that supplementing antibiotic therapy with granulocyte transfusion may help eradicate a resistant organism anticipated to be poorly responsive to antibiotics alone.

Christensen et al⁵⁰ studied 26 infants, all of whom had proven sepsis with some degree of neutropenia (less than 2900 PMNs per microliter).⁵⁰ All underwent bone marrow examinations, and 10 neonates were determined to have had adequate marrow PMN storage pools. These 10 were not considered to be candidates for granulocyte transfusion because of adequate marrow reserves. They were not randomized, and all survived with standard therapy that included antibiotics. The remaining 16 infants were documented to have had markedly diminished marrow PMN storage pools (less than 7% of nucleated marrow cells were postmitotic PMNs) on entering the controlled study. Neonates who underwent transfusion received one granulocyte transfusion containing 0.2×10^9 to 1.0×10^9 PMNs per kilogram of body weight (mean, 0.7×10^9) collected via intermittent-flow centrifugation leukapheresis. All seven neonates in the transfusion group survived, compared with only one of the nine control neonates, indicating that granulocyte transfusion benefits septic neonates who exhibit both relative neutropenia and severely diminished marrow PMN storage pools.

Infants received extensive granulocyte transfusion therapy in the studies by Cairo et al.^{52,53} Those in the granulocyte transfusion group received a course of five transfusions (one every 12 hours); each contained 0.5×10^9 to 1.0×10^9 PMNs per kilogram of body weight collected via continuous-flow centrifugation leukapheresis. In the expanded study,⁵³ survival of infants in the transfusion group (95%) was significantly greater than that of controls.

The results were similar whether considering all infants or only those with culture-proven sepsis. To identify prognostic features, infants who died were found to exhibit lower levels of total hemolytic complement in serum than did survivors ($P < .03$).

Results of two of the controlled trials, reported by Baley et al⁵⁸ and Wheeler et al,⁵⁹ indicated no advantage of antibiotic therapy supplemented with granulocyte transfusion compared with antibiotic therapy alone. Unlike the trials reporting the benefits of granulocyte transfusion, all of which used granulocyte concentrates prepared via automated leukapheresis, both of these studies involved the infusion of granulocytes harvested from units of whole blood. Baley et al⁵⁸ isolated PMNs via centrifugation of fresh, whole blood units, and infused 0.1×10^9 to 0.9×10^9 PMNs per kilogram of body weight (mean, 0.35×10^9) per granulocyte transfusion. Transfusion did not improve survival when results were analyzed for the entire group or for only infants with positive cultures. The study by Wheeler et al⁵⁹ can be easily criticized (few patients were randomized, doses of PMNs were small, and the quality of the PMNs were unsatisfactory). However, two lessons can be learned from this study. First, refrigerated whole blood units are likely to provide unsatisfactory products for transfusion; the mean dose of PMNs per transfusion was only 0.4×10^9 per kilogram of body weight, and the PMNs collected were of poor quality. Second, it is nearly impossible for one institution, despite the best intentions of the investigators, to provide definitive, clinical information. A carefully designed and conducted multicenter trial seems mandatory to provide clear guidance.

Granulocyte transfusions cannot now be firmly recommended to treat neonatal sepsis. However, until more information is available, it seems reasonable to consider supplementing antibiotic therapy with granulocyte transfusion for certain neonates exhibiting strong evidence (either clinically or microbiologically) of bacterial septicemia. To consider granulocyte transfusion, relative neutropenia (less than 3000 PMNs per microliter) must be present, and, in most cases, the marrow PMN storage pool should be diminished (less than 10% of marrow nucleated cells being postmitotic PMNs). The last condition can best be demonstrated with direct examination of the bone marrow. Because it is impractical to always perform a bone marrow examination, some suggest that a tentative estimate can be made indirectly using the differential white blood cell count; thus, diminished storage pools would be indicated when greater than 70% of circulating blood PMNs are immature forms, such as band cells, stabs, or metamyelocytes.^{48,55,61} However, not all agree on the accuracy of this indirect method, and the precise role of the differential white blood cell count in predicting marrow storage pool size requires further study.

The ideal granulocyte product for neonatal transfusions is considered to have these characteristics: volume for infusion of 10 to 15 mL/kg of body weight; dose of PMNs per infusion, 1×10^9 to 2×10^9 per kilogram of body weight; donor seronegativity for hepatitis, cytomegalovirus, human immunodeficiency virus, human T-cell leukemia/lymphoma virus types I and II, and syphilis; and erythrocyte compatibility between donor and neonate. Until more information is available, the granulocyte product of choice is a PMN concentrate prepared via automated leukapheresis.^{60,61} Local practices should be followed regarding the need to irradiate cellular blood products for use in

neonates. Granulocyte concentrates must be infused promptly, certainly within a few hours of donation.

COMMENT

Transfusions of blood components are indispensable to the modern care of critically ill, premature infants. In the future, treatment with recombinant growth factors may decrease the need for homologous blood products. In particular, the treatment of neonatal anemia with erythropoietin seems promising. However, several small studies of such treatment have demonstrated little success.^{62,63} Once problems are resolved to establish the optimal dose, schedule, and route of administration of erythropoietin and to ensure the availability of iron, it seems likely that the need for RBC transfusions will diminish with this treatment.

The best approach now is to transfuse blood components only when they are highly likely to benefit the neonate. Attempts must also be made to select the most effective products from the fewest donors possible. All homologous blood products pose risks, although very small, to the recipient. Remarkable strides have been made recently to diminish these risks in the standard blood supply. These improvements, coupled with the possibility that blood from directed (designated) donors may be less safe than that from volunteer donors, make it mandatory that directed donors be selected with extreme caution.^{17,64} The selection of biological parental donors for neonates may be particularly dangerous because of the alloimmunization of the mother to blood cell antigens inherited by the neonate from the father.^{64,65} Although some would disagree, it is my opinion that directed donors should be avoided whenever possible.⁶⁴ Obviously, this option must be made available when mandated by law and, occasionally, is the most reasonable medical approach (eg, limited-exposure donor programs and difficult compatibility problems). Finally, continued research into the pathophysiology of fetal and neonatal hematopoiesis, the effects of cytopenia (eg, anemia and thrombocytopenia) and the risk-benefit ratio of transfusion therapy is needed to ensure optimal neonatal transfusion practice.

Dr Strauss' research is supported in part by Research Career Development Award K04 HD00255 and Transfusion Medicine Academic Award K07 HL01426 from the National Institutes of Health, Bethesda, Md.

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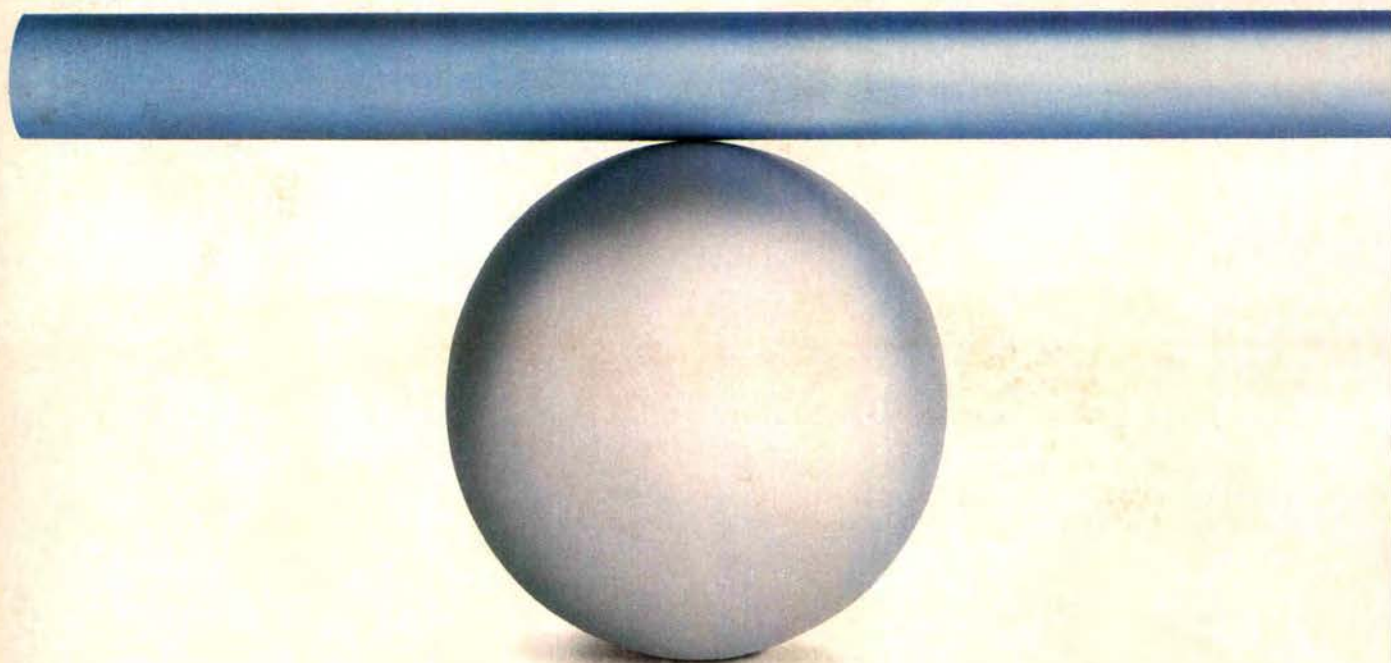
ARCHIVES OF DERMATOLOGY

Anogenital Warts in Children

Matthew H. Kanzler, MD, David C. Gorsulowsky, MD
(*Arch Dermatol*. 1991;127:1063)

An Optimal Balance

Innovation through acellular pertussis technology



Testing the Psychogenic Vomiting Diagnosis

Four Pediatric Patients

Joseph Gonzalez-Heydrich, MD; John Alan Kerner, Jr, MD; Hans Steiner, MD

• We treated four patients with chronic vomiting during childhood in whom a tentative diagnosis of psychogenic vomiting was made after an extensive evaluation. In each case, the diagnosis was reconsidered during the course of treatment, as observations about the patients and their response to interventions accumulated. In three instances, these observations did not fit those expected if the diagnosis of psychogenic vomiting was correct. This led to a reexamination of the organic evaluation and the discovery of an undiagnosed organic contribution to the vomiting. In the fourth patient, gastric emptying studies confirmed that there was a strong psychological contribution to the vomiting, and helped to more carefully define this contribution. Family and individual psychotherapy and treatment were aided by the greater clarity in diagnosis.

(AJDC. 1991;145:913-916)

Chronic unexplained vomiting presents a difficult diagnostic challenge. The differential diagnosis includes organic causes, yet psychogenic disorders are among the most commonly diagnosed. Diagnostic tests, hospitalization, and psychiatric evaluation are associated with certain risks and morbidity, especially in pediatric patients. Thus, the decision as to what tests to perform and when to stop the search for an organic cause is a difficult one. In the presence of obvious psychiatric disease, consideration of organic causes and further diagnostic evaluation may come to a halt. A recent article on the diagnosis and treatment of unexplained vomiting illustrates both the conventional wisdom and some of its difficulties.¹ After a very thorough history, physical examination, blood tests, and radiologic or endoscopic examinations of the upper gastrointestinal (GI) tract, Malagelada and Camilleri¹ recommended, "in the absence of obvious central, labyrinthine, or psychiatric disease, one may proceed with therapeutic trials as outlined above or move on to more specialized investigations, such as gastric emptying stud-

ies and gastrointestinal manometry." Despite a warning in their article that "the presence of neurosis in a patient may be a consequence of the chronic vomiting rather than the cause," in our experience the diagnostic evaluation often does come to a halt when substantial psychopathology is identified. In many instances, this termination of the physical evaluation is appropriate, yet in three of the four patients described herein, all cared for within a 4-month period in the psychosomatic unit at Children's Hospital at Stanford (Calif) University Medical Center, it would not have been. For the fourth patient, continued diagnostic evaluation provided strong evidence of a psychogenic influence on the vomiting and helped direct treatment toward that influence.

PATIENT REPORTS

PATIENT 1.—The first patient was a previously healthy 8-year-old girl whose illness began with substernal pain. She was diagnosed as having bronchitis and was treated with anhydrous ampicillin. One day later, she began to have protracted emesis, syncope, and headache. She was admitted to a community hospital for 2 weeks and was then readmitted for 1 month because of the same symptoms. An initial upper GI series showed a partial small-bowel obstruction, but subsequent upper endoscopy yielded normal findings, except for "increased mucus in the esophagus." Two weeks after her initial radiologic examination, she underwent a complete upper GI series with small-bowel follow-through, the findings of which were interpreted as normal. She underwent extensive evaluation at her community hospital and subsequently at a tertiary care pediatric hospital before she was transferred to the psychosomatic unit at Stanford University Medical Center. These evaluations included abdominal and pelvic computed tomography, abdominal ultrasound examination, electroencephalography, and magnetic resonance imaging of the head, as well as numerous blood chemistry evaluations; all yielded normal findings. At the tertiary care pediatric hospital, the impression of the pediatric GI and neurology services was that the cause of the vomiting was psychogenic. The neurologist suggested to the family that their child might have been sexually abused.

She was transferred to the psychosomatic unit at Children's Hospital at Stanford University Medical Center, a combined psychiatric and pediatric ward. She was receiving nasogastric (NG) tube feeding; previous total parenteral nutrition through a central line had been discontinued because of septicemia. Repeated electroencephalography and a gastric emptying study were performed; both yielded normal findings. A careful physical examination to identify signs of sexual abuse was unrevealing. The

Accepted for publication October 8, 1990.

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patient and her family were evaluated by the family therapy team. The mother was judged to have a borderline personality disorder, and the child was noted to be very depressed. A behavioral "loop" was identified that was thought to explain the child's vomiting. It was observed that when the patient made reasonable demands for her mother's support during conflicts with a sibling, she was reprimanded; however, when she vomited or had abdominal pain, her mother would comfort her. A behavioral program seeking to discourage regressed behavior and reward age-appropriate behavior was instituted, which resulted in some improvement in the child's functioning on the unit; however, the vomiting and complaints of severe substernal pain continued. Meanwhile NG tubes became increasingly difficult to place. The psychiatric resident observed that while treatment directed toward correction of the behavioral loop had resulted in the child exhibiting less regressed behavior, it had not affected the severity of the vomiting. He noted the tremendous difficulty the pediatric team was having placing the NG tubes and did not believe that this could be explained by the child's lack of cooperation. He ordered a barium swallow examination and enlisted the mother's cooperation in getting the child to drink the contrast agent. The barium swallow showed a dilated, residue-filled esophagus with apparent tapering at the gastroesophageal junction. Upper esophagoscopy and esophageal manometry confirmed the diagnosis of achalasia. A review of the radiologic studies from the referring hospitals showed that the two upper GI contrast studies had been performed through an NG tube because the child would not cooperate; thus, the esophagus had not been visualized. On our own unit, the presence of a clear psychiatric disorder in the mother and disturbed family relations delayed the discovery of the diagnosis by 2 months.

PATIENT 2.—The second patient was a 6-year-old girl who was transferred from another tertiary care hospital for investigation of intractable vomiting and abdominal pain that were thought to be psychogenic. During the 15 months before her arrival at Stanford University Medical Center, she was hospitalized four times for abdominal pain, vomiting, and dehydration. Abdominal and head computed tomography, electroencephalography, upper and lower GI series, and blood studies had been performed, but the findings were normal.

During the child's first episode of vomiting, she had been noted to be depressed and was referred to a child psychiatrist. It was noted that her symptoms began soon after the birth of her sister. Also, her mother was depressed for approximately 1 year after the birth and was treated with antidepressant medication. One of the episodes of vomiting that led to hospitalization began the night of her parents' marriage; they had lived together, unmarried, for 10 years. She underwent psychotherapy and was treated with 25 mg/d of imipramine hydrochloride without improvement.

On admission to our psychosomatic unit, she was noted to be very anxious and to have a major depression. She required NG tube feedings and intravenous fluids. A gastric emptying study showed a half-life of 3 hours (markedly delayed), so treatment with metoclopramide hydrochloride was initiated, eventually reaching 0.2 mg/kg per day. Her emesis initially decreased but then worsened. She confided to the nursing staff that her parents beat her and that her father petted her in the genital area. A physical examination revealed bruises on her back, but the genital examination revealed no abnormal findings. The Child Protective Services was called, and the child placed in protective custody.

At this point, the parents became very uncooperative and menacing, and the child's vomiting increased in frequency. Given the allegations of child abuse, the parents' behavior, and the previous organic evaluation that yielded normal findings, a diagnosis of psychogenic vomiting was considered to be likely. It was believed that the vomiting was a symbolic communication and anxiety-binding compromise to deal with the trauma of sexual and physical abuse and/or a somatic manifestation of intense anxiety brought about by the disordered family system and the abuse. The characteristics of the child's vomiting were then reexamined

to see if they fit the above psychogenic diagnosis. The child psychiatry fellow noted the child's complaints of abdominal pain just before vomiting and believed they were not typical of psychogenic vomiting. Thus, she ordered further GI evaluation. A repeated gastric emptying study while the patient was receiving metoclopramide showed delayed emptying, and an upper GI series showed markedly reduced gastric motility. Endoscopy showed esophagitis and reverse peristalsis of the duodenum. As the parents became more calm, the frequency of the child's vomiting decreased so that despite the finding of a physical abnormality, her psychological state also seemed to influence her symptoms. Child Protective Services' protective custody of the child was lifted by court order, and the parents decided to transfer her to another hospital for further evaluation of her vomiting.

Follow-up information from the other hospital revealed a continued pattern of vomiting during the next 2 years, difficulties within the family, and anxiety and depression in the child. The vomiting had resulted in an additional nine hospitalizations during those 2 years, despite continued psychiatric and pediatric interventions. Subsequent to leaving our unit, the patient's esophageal manometry revealed normal findings, but radiologic examinations of the upper GI tract showed a very atonic stomach and a very slow transit time through the small bowel.

PATIENT 3.—The third patient was an 8-year-old girl who suffered from glycogen storage disease type IB, the diagnosis of which had been made at birth. She presented to our child psychosomatic unit after a 2-year history of behavioral problems, culminating in a suicide attempt by disconnecting her NG tube feeding machine. Because of her glycogen storage disease, she was unable to maintain an adequate serum glucose concentration without constant NG tube feedings during the night. Thus, when she disconnected her tube, it resulted in severe hypoglycemia, seizures, and respiratory arrest.

After physical stabilization, she was transferred to our psychosomatic unit. There the myriad of family, social, and individual problems that she was experiencing became apparent; the child psychiatry staff engaged her and her family around these issues. Both the pediatric and pediatric GI services monitored the patient daily and managed her multiple medical problems, which included her glycogen storage disease and its resulting cyclic neutropenia, hyperuricemia, anemia, and multiple infections. Before transfer to the psychosomatic unit, she was noted to have vomiting and abdominal pain. Multiple gastric emptying studies showed either slow but steady emptying or normal emptying. Abdominal ultrasound examinations revealed no abnormalities. Despite treatment with metoclopramide, she continued to vomit two to three times per day, to complain of abdominal pain, and to have diarrhea. Her stools were guaiac positive. Stool examinations for viral and bacterial pathogens yielded normal findings. However, as repeated examinations by both pediatric and pediatric GI teams showed no cause for the emesis and as it remained unresponsive to any treatment, it was ascribed to psychological factors. The milieu staff noted that she vomited when upset about limit setting or about her mother's visits. The vomiting was seen as an expression of her desire to strike out at milieu staff and at her mother. She was encouraged to express her feelings verbally instead of by vomiting.

This situation continued until 2 months after admission. The psychiatry resident made a flow chart of the number of emesis episodes and stools per day vs maternal visits. When no correlation was found, the resident asked the pediatricians to reexamine the child for organic causes of vomiting. When a physical examination revealed no organic cause, the psychiatry resident again reviewed the results of the studies performed to date and, noting that it had not been done yet, he ordered a stool ova and parasite examination. The stool was shown to be harboring *Giardia lamblia*, and the patient was treated with oral furazolidone for 7 days. Her emesis and diarrhea improved, but her psychiatric difficulties persisted. She was not discharged from the unit for another 2 months.

PATIENT 4.—The fourth patient was a previously healthy 7-year-old girl who was admitted to our psychosomatic unit after four hospitalizations and an extensive pediatric evaluation in her community failed to identify a cause of her vomiting. Her weight had decreased from 21.6 to 15.3 kg since the onset of her illness. The only abnormal finding from her diagnostic evaluation was some mild inflammation of the gastroesophageal junction found at biopsy with otherwise normal endoscopic findings. A stool examination revealed no parasites but was positive for rotavirus 1 month after the illness onset. Head computed tomography demonstrated an Arnold-Chiari malformation type I, and magnetic resonance imaging of the head showed slightly enlarged cerebellar tonsils. On admission to our pediatric psychosomatic unit, it was noted that since the onset of this child's illness, there had been increased stress at home. A mental status examination revealed a tearful, very withdrawn, and anxious child. She continued to vomit to the point that she needed parenteral nutrition. A gastric emptying study showed mild delay, and metoclopramide was prescribed. Because her father was perceived to be intrusive, sexual abuse was suspected. An investigation revealed no evidence of sexual abuse. However, during the investigation, which lasted 1 week, her parents were not allowed to visit her. During this time, she stopped vomiting, began to eat, and became outgoing, active, and assertive. After the parents were allowed to visit again, vomiting resumed, and she became withdrawn. A repeated gastric emptying study showed marked delay. Because the father was present during the test and was noted to be extremely intrusive and anxious, the gastroenterologist requested that it be repeated with the father absent. This was done, and the test revealed normal findings just a few hours after the previous test. The father's level of intrusiveness and the family's general level of stress were addressed in family therapy, with improvement in the child's vomiting. A couple of days before discharge, the child expressed apprehension and began vomiting again. She was transferred back to her community hospital, where she and her family continued individual and family therapy.

COMMENT

Although psychogenic vomiting is frequently diagnosed, it has received relatively little attention in the literature. Those reports that have been published seem to fall into one of two categories: (1) case reports and commentaries emphasizing psychodynamic, family systems and cultural causes, with the treatments targeted accordingly,²⁻⁷ and (2) case series demonstrating organic disease in individuals diagnosed as having psychogenic vomiting.⁸ The researchers in the first category have emphasized the role of stress in causing psychogenic vomiting and have described many sources of that stress. These investigators have called attention to the presence in some of their patients of a perception of being trapped in a hostile relationship,² cultural or family dynamic conflicts,³ and emotional upset or profound psychic disturbance within the vomiting individual.⁴ They have also proposed some predisposing factors, including parental loss, a family history of vomiting,² and prolonged symbiotic relationships with a failure of separation individuation in the child.⁵ In addition Rosenthal et al⁶ and Wruble et al⁷ have described the natural history of psychogenic vomiting and noted that, at the time of follow-up, almost all patients are improved but still vomiting, regardless of whether or not they received psychotherapy. There are several problems with this literature, however. There is no way offered to distinguish whether the conflicts described above in the individual and the family are causing the vomiting, are themselves the result of the chronic vomiting, or simply coincident with it. Another problem is in the definition of psychogenic vomiting as vomiting for which no

physical cause can be found.⁴ This presumes that, with our present technology, we are able to detect all organic abnormalities that can cause vomiting.

Among authors who are skeptical of the diagnosis of psychogenic vomiting, Stacher⁸ describes 58 patients referred for either dysphagia or chronic vomiting and in whom the condition was thought to be psychogenic by the referring physicians. He reported that all were found to be suffering from organic disorders: achalasia, esophageal motility disorders, gastric ulcer, or gastroesophageal reflux. A problem with this analysis is that it is unclear whether the motility disorders are the only factor influencing the vomiting or whether psychological factors could be influencing the vomiting despite the presence of organic disease.

Recently, Abell and coworkers⁹ examined eight adults with recurrent cyclic vomiting in whom no demonstrable lesions were found either in the gastrointestinal tract by endoscopy and barium studies or in the central nervous system by computed tomography or electroencephalography. All eight had abnormalities of gastrointestinal motility during an asymptomatic period—gastric hypomotility in five, small-bowel dysmotility in six, delayed gastric emptying in two, and gastric dysrhythmia in two. Abell and coworkers concluded that idiopathic cyclic nausea and vomiting may be related to altered gastrointestinal motility. However, of five patients who underwent psychological evaluation, one was diagnosed as having depression and two others were thought to have psychosomatic preoccupation on the basis of the Minnesota Multiphasic Personality Inventory. An editorial¹⁰ in the same journal issue described the confusion that exists in the basic concept of "functional" gastrointestinal disease, especially in light of recent data that an organic basis, such as vagal neuropathy¹¹ or autonomic denervation,¹² may exist for the development of the irritable bowel syndrome. As stated previously, even in patients with documented motility abnormalities, it may be that these are not the only cause of the recurrent vomiting symptoms.

As the above-mentioned reports illustrate, the literature on psychogenic vomiting parallels the archaic organic/functional dichotomy that until recently dominated medicine and psychiatry. Interactions between stress and a gastrointestinal system with a low threshold for vomiting are not emphasized. The implication is that cases can be neatly separated into organic or functional vomiting and that the diagnosis of psychogenic vomiting is strictly one of exclusion. No way of making the diagnosis of psychogenic vomiting on the basis of an abnormal finding is offered nor are criteria offered for the rejection of the psychogenic diagnosis when the organic evaluation yields normal findings.

An underlying assumption of the articles that discuss psychogenic vomiting from a psychological perspective seems to be that we are able, with our present technology, to detect all organic contributions to the vomiting. The assumption of the article discussing psychogenic vomiting as misdiagnosed organic vomiting seems to be that if an abnormality is found on a physical test, then there is no psychogenic contribution to the vomiting. In our opinion, neither of these assumptions is warranted. The four patients described above demonstrate some of the pitfalls of these assumptions and the dualistic paradigm underlying them. They also illustrate some different ways to proceed diagnostically.

All four patients underwent extensive inpatient pediatric scrutiny for several months before objective evidence for an organic contribution to their vomiting surfaced. For the first patient, the substantial psychiatric dysfunction in the family and child contributed to the omission of an important early step in the evaluation of chronic unexplained vomiting: visualization of the esophagus during the upper GI study. Our patient would not swallow the contrast material, and the child psychiatry team needed to enlist the mother's help in getting the child to cooperate. Moreover, the psychiatry resident had to draw on his experience in psychiatrically and medically treating children to realize that the psychogenic hypothesis could not explain how a child (no matter how oppositional and stubborn) could impede the downward progress of an NG tube once it was in the esophagus. In this case, psychiatric and organic disease coexisted. It should be noted that the endoscopy at our hospital during which achalasia was noted took place 3 months after the study performed at the outside hospital, during which only increased mucus was noted. Either the outside hospital study was in error or the achalasia was very early in its evolution at the time of the initial study.

For the second child, objective evidence of a physical abnormality was also found. Again, the preponderance of psychiatric disease in the child and family as well as the timing of the onset of symptoms would have led many reasonable clinicians to abandon the consideration of an organic cause after the extensive initial evaluation revealed no abnormality. Yet the physician treating the child, because she had pediatric and psychiatric experience treating children, was able to press for further work-up when the psychogenic hypothesis could not fully explain the observed characteristics of the child's vomiting. The third child's history, in addition to illustrating the above points again, also shows the dangers of relying too heavily on correlations between variables such as maternal visits and vomiting that are casually observed rather than formally tested against the documentation in the chart.

The findings of the fourth child's evaluation illustrate how vomiting can be a somatic manifestation of stress. The gastroenterologist subjected this hypothesis to a rigorous test. The reasoning behind this test is as follows: if the stress the child is feeling is contributing to her vomiting because it is slowing the transit through her stomach and if a major part of her stress is being caused by the immediate intrusiveness of her father, then one may predict that if the father leaves the room, then the child's gastric emptying might improve. The findings confirmed the hypothesis and aided in guiding treatment and strengthening the treatment alliance with the family. For all four children, the child's psychologic state and the contingencies impinging on their behavior were observed to influence the severity of the vomiting. Thus, one should avoid the trap of reductionism.

If the history of these four children and our review of the literature contain any lessons for those faced with similar diagnostic conundrums, they might be as follows: First, constantly rethink the diagnosis. If the primary diagnosis is organic, can dynamic, interpersonal, or environmental factors be contributing as well? If the primary diagnosis is psychogenic, could psychopathology in the patient or family have sabotaged the organic evaluation? Could the limitations of the available technology allow one

to miss an organic disease? Could a previously undiagnosable disease, organic or psychologic, become more apparent with time? Thus, it is imperative that the clinician supervising the care of these patients have a firm grasp of physical medicine and psychology. Also, it is important that psychiatry and pediatrics work together as a team and pool their experience to think through these patients' evaluations.

Second, make predictions based on the diagnosis of what you would expect to see in the history, presentation, laboratory examinations, and response to treatment; then, test these predictions. If the diagnosis is psychogenic, three constellations need to be distinguished and looked for, alone and in combination: (1) vomiting as a symbolic communication and anxiety-binding compromise (for this constellation, one needs to be able to demonstrate a conflict, a traumatic event and primary and secondary gain); (2) vomiting as a willful, manipulative act (malingering, Munchausen syndrome, and Munchausen syndrome by proxy); and (3) vomiting as a somatic equivalent of anxiety, ie, a nonspecific, nonsymbolic expression of current conflict.

The possibility must always be entertained that psychiatric and pediatric diseases coexist and interact without any causal connection. Positive evidence for each of these should be looked for, and the clinician should also think about what would suffice to convince him or her to abandon the diagnosis. Last, we would emphasize again that as true psychiatric disease makes the orderly pursuit of an evaluation much more difficult, the presence of definable psychiatric disease should lead the clinician to intensify rather than relax his or her scrutiny of the differential diagnosis and adequacy of the organic evaluation.

The authors thank Mark Perl, MD, for his advice and comments on the manuscript and Darcia Elliott for editorial assistance.

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A Practical Guide to Successful Breast-feeding Management

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● It is often difficult for new mothers to know whom to approach for the necessary guidance and practical problem solving required for successful long-term lactation. Although obstetricians are familiar with the care of the breast, they may not maintain the degree of postpartum follow-up necessary to ensure its proper function nor is it their responsibility to ensure that the infant receives proper nourishment. Pediatricians are expected to offer advice and information regarding not only the advantages and disadvantages of breastfeeding but also practical management of this art. We provide a guide for practitioners who wish to assist breast-feeding mothers and their infants.

(AJDC. 1991;145:917-921)

Demonstrable knowledge regarding breast-feeding and experience in counseling nursing mothers are important to parents and contribute to their selection of a primary care pediatrician. Unfortunately, few house staff training programs provide sufficient education about this physiologic function. As a result, most pediatricians today enter practice unaware of how to manage the common problems of breast-feeding, such as cracked nipples, poor latch-on, mastitis, and supplemental feeding. When confronted with lactation difficulty in a new mother, many find it easiest to recommend formula to prevent further problems.

Historically, it has not always been incumbent on the pediatrician to be well versed in the practical management of lactation. In past generations, breast-feeding was handled within the extended family, and the art was passed from mother to daughter. However, in the early 1950s, the incidence of breast-feeding in the United States began to decrease, and formula feeding became the predominant mode of infant feeding. This was a result of the development of safe and affordable infant formulas, complex social and cultural pressures influencing women, and the failure of the medical profession to promote the benefits of breast-feeding.¹ The incidence of breast-feeding in-

creased during the 1970s and peaked in the mid-1980s. Nationwide figures for 1983 indicated that 62% of women chose to breast-feed their newborns.² These figures may be somewhat misleading, as studies tend to define breast-feeding as nursing at least once per day. Therefore, the incidence of exclusive breast-feeding in the first few months after birth may be lower. To increase the incidence of breast-feeding, pediatricians must possess greater knowledge of the practice of this art, the difficulties that may be encountered, and the solutions to those difficulties.

Our objective is to provide resident physicians-in-training with a practical guide for counseling about breast-feeding in the prenatal and postnatal periods.

PREPARATION FOR BREAST-FEEDING

The initial contact pediatricians have with a new mother is usually during the third trimester of pregnancy at the prenatal interview. This is an ideal time to inquire about choice of infant feeding and to reinforce breast-feeding when appropriate. Although some studies have shown that infant feeding decisions are made before the third trimester,³ choices may have been influenced by certain misconceptions or fears held by the expectant mother or father. Some of these commonly held misconceptions and fears regarding breast-feeding are summarized in Table 1. Pediatricians should discuss these fears and any differences of opinion between parents over preferred feeding methods. The parents' attitudes and opinions should be explored so that myths can be openly dispelled.

The American Academy of Pediatrics recommends exclusive breast-feeding during the first 6 months of life. Benefits to the child from breast-feeding, such as improved mother-infant bonding; reduced incidence of gastroenteritis and otitis media; reduced frequency of hospital admissions; protective immunity against fungal, viral, and bacterial infections; and reduced incidence of allergic diseases, should be presented.⁴⁻⁸ However, when informed parents decide against breast-feeding, it is important for the pediatrician to support them. Pediatricians should encourage prospective mothers to attend classes on breast-feeding, because the likelihood of breast-feeding success is increased by providing mothers with specific knowledge about breast-feeding and the support of other nursing mothers.⁹ Pediatricians should become familiar with

Accepted for publication January 3, 1991.

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Table 1.—Some Commonly Held Misconceptions and Fears Regarding Breast-feeding

1. Inadequate milk supply secondary to small breast size.
2. Loss of sexual breast activity during lactation.
3. Cosmetic breast changes as a result of lactation.
4. Previous generation failure of breast-feeding.
5. Poor nutritional content of breast milk ("not rich enough").
6. Difficulty in learning how to breast-feed.
7. Disapproval of spouse.
8. Poor public acceptance.
9. Loss of freedom or spontaneity.

local community breast-feeding support groups and encourage parental participation. Pediatricians should advocate the assistance of lactation support teams that are currently employed in many hospitals to assist new mothers before discharge. Frequently, the pediatrician's office personnel are the initial contact for mothers who call with lactation problems. Therefore, the office staff should be appropriately trained regarding lactation management.

A thorough understanding of specific problems commonly encountered by breast-feeding mothers, together with proper intervention and treatment, is required to provide adequate support and counseling to breast-feeding mothers.¹⁰ Prenatal interviews and discussions with expectant mothers will serve to define their knowledge base and to uncover potential problems.

PRENATAL CONCERNS

Inverted Nipples

Although a substantial number of problems encountered in breast-feeding are due to variant nipple morphologic features, such as flat or inverted nipples, pediatricians do not examine the breasts of an expectant mother during a prenatal interview. The normal nipple may be flush or confluent with the areola but will become erect with the stimulation provided by the newborn's sucking. The inverted nipple will retract into the areola when pinched between the thumb and index finger. Ideally, this condition should be identified prenatally so that proper measures can be instituted to prepare the nipple.¹¹

Pediatricians may elicit a history of inverted nipples by asking if there have been difficulties with nursing previous infants, or they may wish to show mothers pictures or drawings of different types of nipples and ask which type appears most similar to their own. If a history of any nipple and/or breast abnormality is elicited, communication with the mother's obstetrician should be considered.

Breast shields and breast shells are corrective devices that fit over the nipple and are worn underneath the bra. They are readily available at pharmacies or maternity stores and should be worn daily during the third trimester by women with inverted nipples. Hoffman's¹² exercise is a useful additional therapy, in which the forefingers are placed at opposite locations on the areola margins and then pulled outward. This procedure should be performed several times daily. Both of these interventions may be continued after birth should flat or inverted nipples not be fully corrected by the time of delivery. Occasionally, changes in nipple contour will not occur until after suckling has begun.

Nipple Preparation

Preparation of the nipple has been recommended by various sources, although the efficacy of such practices has

not been shown.^{11,13} Some popular techniques, including harsh rubbing or the use of soaps containing irritants, can dry or crack nipples. Creams and lotions for the breast may also be detrimental. In reality, specific intervention for the normal nipple is unnecessary.

Previous Breast-feeding Experience

For various reasons, some mothers may have experienced difficulty breast-feeding an infant in the past. This can produce anxiety or reluctance regarding their future attempts. A careful history to elucidate the nature of the previous problem and evaluation of its relevance to future attempts is essential. These mothers may be insecure and may question the physician frequently regarding whether the infant is receiving sufficient milk. These mothers will benefit from additional support and positive reinforcement.

POSTPARTUM PERIOD

Duration and Frequency

Suggested durations for nursing at each breast range from 3 minutes to 20 minutes.^{1,12} The American Academy of Pediatrics recommends a nursing duration of up to 10 minutes on the first breast and up to 20 minutes on the second breast. However, exact times should not be recommended, as time may vary with each individual infant and many newborns are too sleepy in the first few days after birth to achieve long nursing durations. Proper latch-on techniques are important to facilitate breast stimulation and to hasten the let-down reflex.¹⁴ Although glucose water following nursing continues to be routine on (too) many neonatal services, it is unnecessary, because breast milk contains sufficient water for the normal newborn infant. In fact, supplemental feedings of sterile or glucose water should be discouraged during the first few days of nursing, as they may reduce milk production and increase neonatal jaundice. Instead, mothers should be instructed to nurse more frequently to enhance milk supply, even as often as every 2 to 3 hours (eight to 12 times per day). In addition, the early introduction of a bottle may result in nipple confusion.

In most cases, supplemental feeding should be avoided to prevent nipple confusion and suppression of milk production. However, a mother who experiences extreme exhaustion or who has received medication before or during delivery may be physically unable to nurse her child eight to 12 times per day. Also, certain infants (such as those with low birth weight) may be at increased risk for hypoglycemia if feedings are diminished. In those situations, supplemental feeding with formula may be necessary. If supplemental feedings are begun, they should be rapidly weaned once the specific indication for their initiation has resolved.

Initially, infants should be nursed on demand. Both breasts should be nursed at each feeding to ensure bilateral breast stimulation and sufficient infant intake. To prevent engorgement, the first breast for each feeding should be the last breast offered during the prior feeding. Many mothers find that placing a small safety pin on the side of the bra on which the next feed will begin is a helpful reminder. Newborns demand feedings every 1.5 to 3 hours throughout the day and night. Long intervals between feedings should be discouraged initially. Most mothers need reassurance during the early postpartum period that a better schedule will occur later.

Positioning

Fortunately, several available brochures and manuals contain photographs and illustrations of proper nursing

Table 2.—Management of Breast-feeding Jaundice^{15*}

- | |
|--|
| A. Early onset (starts 3 to 4 days post partum): "jaundice in a breast-fed infant" |
| 1. Encourage mothers to nurse frequently (minimum 8 times per day). |
| 2. Avoid formula supplementation, unless milk production is inadequate. |
| 3. Do not use glucose water or sterile water supplementation. |
| 4. Monitor serum bilirubin concentrations daily on an outpatient basis. |
| 5. Mothers may use mechanical or manual methods to express their milk after feedings to increase milk volume. |
| B. Late onset (starts 7 to 10 days post partum): "breast milk jaundice" |
| 1. If the bilirubin concentration reaches 290 to 342 $\mu\text{mol/L}$, breast-feeding should be interrupted for 48-96 hours with formula given as a diagnostic test. |
| 2. Instruct mothers to maintain lactation with manual or mechanical methods of milk expression during the interruption. |
| 3. Monitor serum bilirubin concentrations every 12 to 24 hours. |
| 4. Resume breast-feeding after a decrease in serum bilirubin concentration confirms the diagnosis. |

*For conversion of serum bilirubin, 1 $\mu\text{mol/L}$ = 0.06 mg/dL.

positioning.^{1,12,14} The most commonly used position involves cradling the infant in the crook of the mother's arm, with the infant's head aligned with the breast. The infant should be lying on his or her side with the mouth directly in front of the nipple. The infant's lower arm can be tucked under the torso or around the mother's side to keep the area clear of distraction or obstacle. The breast should be cupped with the mother's free hand with use of the first and second fingers to grasp behind (posterior to) the areola. The nipple alone should not be offered to the infant; instead, both the nipple and areola should be offered. Alternate positions for nursing include the "football hold" (head in the palm of the hand with the infant's body supported by the mother's forearm and the side of the torso) and the recumbent position.

Latch-on

As much of the nipple and areola as possible should be inserted into the infant's mouth. Allowing the infant to suck only on the nipple leads to cracked, sore, and bleeding nipples (problems discussed in the following section). After latch-on, the mother may use her free hand to gently press down on the part of her breast near the infant's nose to ensure adequate clearance for unlabored respiration. Removal of the infant from the breast is accomplished best by inserting a finger into the infant's mouth between the gums to break suction. This technique effectively prevents nipple traction or trauma.

EARLY PROBLEMS Jaundice

Breast-feeding jaundice can be categorized as early-onset jaundice in a breast-fed infant (occurring 3 to 4 days post partum) and late-onset breast milk jaundice (occurring 7 to 10 days post partum). The cause of early-onset breast-feeding jaundice, "jaundice in a breast-fed infant," is related to infrequent feedings, lack of demand feedings, and inadequate energy intake.¹⁵ Frequent feedings will stimulate gut motility and decrease the intestinal absorp-

tion of bilirubin by decreasing enterohepatic circulation. Contrary to common belief, sterile water or glucose water supplementation of breast-fed infants does not reduce bilirubin concentrations.¹⁶

This condition should be anticipated when mother and infant are discharged from the hospital within 48 hours of delivery. Often, it can be prevented with appropriate lactation counseling. It is very important for diagnosis to obtain a detailed history, which should include the number of feedings in the last 24 hours, the number of wet diapers, the number of stools, feeding vigor, and the amount of supplementation, if any.

The management strategies for early and late breast-feeding jaundice are summarized in Table 2. Mothers of infants with early-onset jaundice should be encouraged to nurse as frequently as possible, especially if the bilirubin level is rising.¹⁷ In an otherwise healthy infant, outpatient bilirubin determinations may be obtained if other causes of pathologic jaundice are excluded. It is important not only to determine the bilirubin concentration but also to ensure adequate milk intake by the infant. If there is a concern that the mother's milk supply is inadequate, she should be encouraged to express her milk manually or mechanically after each nursing episode to increase stimulation and thus milk production. During that time, the infant should receive a milk-based formula after each suckling. This should be continued until it is determined that the mother has an adequate milk supply.

The cause of late-onset breast-feeding jaundice, "breast milk jaundice," originally was attributed to a hormone in breast milk that inhibited glucuronyl transferase. Studies have been contradictory, with some supporting this association and others failing to do so. Recently, other studies have demonstrated an enhancement of enteric bilirubin absorption in breast-fed infants with jaundice as a result of increased concentrations of long-chain nonesterified fatty acids and human milk lipoprotein lipase. The timing of onset is probably related to the fact that lipoprotein lipase level is not elevated in human milk until after the fourth postpartum day.¹⁷ It has also been demonstrated that the milk from mothers of infants with breast milk jaundice will enhance intestinal bilirubin absorption.¹⁷ The process can be blocked with milk-based formula feeding.¹⁷ It appears that the causes may include an abnormality in the milk and in the recipient host, so that bilirubin absorption continues unimpeded.¹⁷ A definite cause, however, has not been firmly established.

Late-onset breast-feeding jaundice usually peaks by days 10 to 15 and is noted clinically during the second and third week of life. Jaundice may persist for 27 to 80 days,¹⁸ but usually the serum bilirubin is below 86 $\mu\text{mol/L}$ by the end of the third week. When the serum bilirubin level exceeds 290 $\mu\text{mol/L}$, breast-feeding should be interrupted for 1 to 4 days (usually 48 hours) and a milk-based formula substituted as a diagnostic test. Serum bilirubin will decline by 50% during this period if the elevation was a result of breast milk jaundice. Realizing that kernicterus has never been reported in an infant with breast-feeding jaundice, some physicians prefer waiting until the serum bilirubin concentration approaches 342 $\mu\text{mol/L}$ before interrupting nursing.^{17,19} If the serum bilirubin level does not decline as a result of interruption of nursing, breast-feeding should be resumed during the search for a cause of the jaundice. Nursing should not be interrupted if a separate cause for hyperbilirubinemia is identified. Again,

during any period of nursing interruption, mechanical methods of milk expression should be utilized. In all situations, documentation of the rationale for continuing breast-feeding in the presence of jaundice should be made in the patient's chart.

Engorgement

Breast engorgement is an uncomfortable and sometimes painful swelling of the breasts that occurs commonly on the second to seventh postpartum days. It is due to increased blood and lymph flow to the breast at the onset of lactogenesis. Poor or infrequent emptying of the breast can compound this problem. Fortunately, this condition is easily managed by frequent emptying of the breast by feeding or by mechanical or manual methods of milk expression during times of mother-infant separation. Additional comfort may be provided by warm, moist compresses and warm showers, which aid in milk flow, and by hand expression of milk before nursing, which softens the areola and allows for easier infant latch-on.

Sore Nipples

Commonly, the initial grasp and suck of the nipples will cause pain during the first few days of lactation. This sensation is the result of negative pressure on the still-empty ductules. Sore nipples can be exacerbated by incorrect latch-on or impairment of milk let-down. Usually, this condition begins during the first few days of lactation and is greatest at the beginning of feeds. Once lactation is well established, the tenderness diminishes; therefore, treatment is simply supportive.

Cracked or fissured nipples are usually the result of improper latch-on, improper disengagement, or the use of abrasive soaps or alcohol. Treatment of this condition involves rinsing the nipples with water and allowing thorough air drying after nursing. Once the nipples are dry, a small amount of milk should be expressed, gently rubbed onto the nipples, and allowed to air dry. Prolonged nipple exposure to air will augment healing. When severe discomfort from fissuring occurs, nipple shells with a large back may be worn between feedings to prevent the nipple from rubbing on the bra. If infection of the nipple is a possibility, topical antibiotics may be applied but should be washed off before nursing.

Late onset (>1 month postpartum) or chronically sore nipples causing burning pain throughout the breast is often the result of *Monilia* infection. There is often concomitant thrush or fungal diaper rash in the infant. Treatment of both maternal and infant sources of infection with topical antifungal agents, coupled with meticulous air drying of the nipples, is required.¹

Appetite Spurts

Appetite spurts are periods of crying and apparent insatiability on the part of the infant. The infant nurses more frequently and for longer periods but still seems hungry.²⁰ The episodes usually occur at 8 to 12 days, 3 to 4 weeks, and 3 months of age, and at variable times thereafter. Appetite spurts can be very frustrating for the mother, who may feel inadequate because she perceives herself as failing to satisfy her child. They are usually able to be differentiated from colic based on their occurrence at the previously stated ages. Many physicians are tempted to recommend supplemental formula feeding at this time, but this will only intensify the problem. The mother's milk

Table 3.—Danger Signs of Possible Inadequate Milk Supply in First 2 Weeks

1. Less than 6 wet diapers per day (normal, 6 to 8/d).
2. Stool frequency of less than 4 per day (normal, 6 to 10/d).
3. Continual crying and apparent hunger.
4. Infant refusal to latch on.
5. Continually sleepy infant.
6. Nursing frequency of less than 7 feedings per day.
7. Frequent formula supplementation.
8. Jaundice.
9. Body weight loss of $\geq 10\%$.
10. Long nighttime intervals without feeding.
11. Maternal fatigue/anxiety.

production should meet the increased demand within 3 to 5 days of increased stimulation from the hungry infant. Supplemental formula feedings will satiate the infant but decrease the suckling time, resulting in insufficient stimulation of the breast and inadequate milk production. Physicians should recommend frequent feedings of eight to 10 times per day during these periods.

Plugged Ducts

Plugged ducts are focal areas of breast engorgement usually caused by stasis of milk. The condition results from irregular nursing, skipped feedings, or inadequate emptying of the entire breast and may occur at any time during lactation, although it is most common during the first 3 months. Treatment involves starting consecutive feeds on the affected side and changing nursing position often to help facilitate emptying of different lobes of the breast. Additional relief is provided by gently massaging the affected area during nursing or pumping while applying moist heat. Frequent nursing should also be recommended.

Mastitis

Mastitis is a cellulitis of the interlobar connective tissue of the breast. Affected women will experience breast pain, swelling, erythema, and fever. The infection is usually due to *Staphylococcus aureus* and occasionally to *Streptococcus* species. Mastitis may occur anytime during lactation but rarely occurs before 2 weeks post partum. A plugged duct is a frequent precursor of infection.

Antibiotic therapy with oral antistaphylococcal medication should be instituted promptly. Bed rest and moist heat application provide symptomatic relief. Most important, nursing should not be stopped during treatment. Feedings should be initiated on the unaffected breast and the infant switched to the affected side only after let-down occurs.

DANGER SIGNS

The danger signs manifested by an infant who is not receiving an adequate milk supply are summarized in Table 3. These signs often become apparent during the interval between hospital discharge and the first physician's office visit, 1 to 2 weeks after birth. Therefore, telephone or office contact with a knowledgeable source at approximately 3 to 5 days after birth is essential to determine the adequacy of the mother's milk supply, to provide support and encouragement to the lactating mother, and to identify any problems. It is essential that a nursing mother's

initial contact be with personnel trained in breast-feeding management. Therefore, pediatric office staff should be encouraged to attend lactation seminars to develop and maintain their skills at recognizing danger signs.

CONCLUSION

Health professionals in general, and pediatricians in particular, are expected to provide guidance before and during lactation to increasing numbers of breast-feeding mothers. This need for professional guidance will continue as long as traditional and historical support systems for new mothers remain generally unavailable. We, as pediatricians, need to become familiar and comfortable with the role of counselor and adviser for nursing mothers. This role will allow us to place an increased emphasis on well-child and preventive care. It will give us another avenue to help prevent disease, rather than only treat it once it occurs. Moreover, the role will offer us participation in one of the most rewarding experiences in the lives of parents and their infants.

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Predicting Risk of *Pneumocystis carinii* Pneumonia in Human Immunodeficiency Virus–Infected Children

Richard M. Rutstein, MD

• Effective prophylaxis exists against *Pneumocystis carinii* pneumonia, a major cause of illness and death among human immunodeficiency virus–infected children and adults. While adults with CD4 counts less than $0.2 \times 10^9/L$ are at highest risk for *Pneumocystis carinii*, clinical or laboratory markers of high risk in children infected with the human immunodeficiency virus have not yet been established. A chart review of 13 infants with perinatally acquired human immunodeficiency virus infection and children with *Pneumocystis carinii* pneumonia revealed that infants younger than 12 months developed *Pneumocystis carinii* pneumonia despite CD4 counts that were normal by adult standards. In contrast to the markedly increased serum IgG levels seen in most children infected with the human immunodeficiency virus, five children with *Pneumocystis carinii* pneumonia had IgG levels less than 3.0 g/L. Twelve patients had pre-existing symptoms consistent with human immunodeficiency virus infection before the episode of *Pneumocystis carinii* pneumonia. In addition to clinical symptoms, low IgG levels and CD4 counts adjusted for age may serve to identify those children who are most at risk for *Pneumocystis carinii* pneumonia and therefore candidates for prophylaxis. Prophylaxis should be offered to all infants under age 12 months with proven, or clinical symptoms compatible with, human immunodeficiency virus infection. For children older than 12 months, CD4 counts less than $0.3 \times 10^9/L$ appear to be predictive of risk for *Pneumocystis carinii* pneumonia, and these children should also receive prophylaxis.

(AJDC. 1991;145:922-924)

Pneumocystis carinii pneumonia (PCP) represents a leading cause of morbidity and mortality in individuals infected with human immunodeficiency virus (HIV). More than 75% of adults with HIV will ultimately develop PCP¹; as many as 20% will succumb during the first episode. In children with HIV infection, PCP is the most common opportunistic infection and associated with a median survival of only 1 month from the time of diagnosis.²

Effective prophylaxis against PCP has been demonstrated in studies of adults with HIV infection and children

with cancer undergoing chemotherapy.³⁻⁷ The agents most commonly employed are aerosolized pentamidine and oral trimethoprim/sulfamethoxazole.

Optimal treatment of HIV-infected individuals includes the determination of relative risk for a first episode of PCP and the initiation of chemoprophylaxis if indicated. The adults at greatest risk, with a 20% yearly incidence of PCP, have absolute CD4 counts lower than $0.2 \times 10^9/L$.⁸ For these patients, the Centers for Disease Control advises prophylaxis with aerosolized pentamidine or trimethoprim/sulfamethoxazole.⁹ In children with HIV, there are no published data on primary prophylaxis against PCP or on markers for those most at risk of developing the disease. One recent article and several abstracts indicate that the CD4 count is not as useful in children as in adults.¹⁰⁻¹³

To further investigate clinical and laboratory markers useful as indicators of risk of PCP in HIV-infected children, a retrospective chart review was conducted.

SUBJECTS AND METHODS

I reviewed the charts of patients congenitally infected with HIV who were treated at the Children's Hospital of Philadelphia (Pa) from January 1985 to March 1990. Thirteen patients had histologically proven PCP (by bronchopulmonary lavage or biopsy). T-cell ratios, absolute CD4 counts, IgG levels, and presence of HIV-related preexisting symptoms were noted. T-cell subsets were determined using whole blood specimens stained with monoclonal antibody directed against the desired subset. The specimen was then run through a flow cytometer and the number of stained cells counted. Patients were classified according to the Centers for Disease Control pediatric HIV guidelines.¹⁴ In 11 of the 13 patients, the CD4 counts and IgG levels were obtained 1 week to 3 months before the diagnosis of PCP. In two patients who first presented with acute PCP, the studies were performed at the time of hospitalization and diagnosis of PCP.

RESULTS

Age at diagnosis of PCP ranged from 3 months to 9 years. These 13 patients represented 26% of the HIV-infected symptomatic children (P2A symptomatic, non-specific findings or acquired immunodeficiency syndrome-defining illness)¹⁴ followed up at our institution during the study period. Five patients died of PCP. All three children older than 12 months had absolute CD4 counts of less than $0.3 \times 10^9/L$ at the time of PCP diagnosis (at ages 14, 31, and 102 months).

All 10 patients younger than 12 months had CD4 counts higher than $0.25 \times 10^9/L$; eight had absolute CD4 counts

Accepted for publication January 28, 1991.

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Reprints not available.

Table 1.—Signs or Symptoms of Human Immunodeficiency Virus in 13 Patients Before Presentation With *Pneumocystis carinii**

Patient No./ Age, mo†	Symptoms*	CDC Classification‡	CD4-CD8 Ratio	Absolute CD4, $\times 10^9/L$	IgG, g/L	Outcome
1/3	FTT, UTI	P2A	0.3	0.712	2.94	Died
2/3	None	P-O	0.5	0.350	19.00	Died
3/5	Recurrent <i>Salmonella</i> bacteremia	P2D1	2.4	1.600	2.69	Survived
4/6	Recurrent bacterial disease	P2D2	0.8	1.030	2.36	Survived
5/6	Recurrent thrush	P-O	0.2	0.284	13.80	Survived
6/7	FTT, thrush, <i>Candida</i> esophagitis	P2D1	1.8	1.000	1.90	Died
7/7	FTT, adenopathy, hepatomegaly	P2A	2.2	0.700	6.78	Survived
8/8	FTT, UTI, thrush	P2A	0.7	2.000	23.00	Survived
9/9	CMV retinitis	P2D1	0.3	0.770	4.38	Died
10/9	Adenopathy, hepatomegaly	P2A	0.5	1.875	20.80	Survived
11/14	Hepatitis, <i>Candida</i> esophagitis	P2D1	0.1	0.130	1.95	Died
12/31	FTT, CNS, LIP	P2BC	0.3	0.269	32.00	Survived
13/102	MAI, LIP	P2CD1	0.1	0.108	10.20	Survived

*FTT indicates failure to thrive; UTI, urinary tract infection; CMV, cytomegalovirus; CNS, progressive encephalopathy; MAI, disseminated *Mycobacterium avium/intracellulare*; and LIP, lymphocytic interstitial pneumonitis.

†At time of diagnosis of *Pneumocystis carinii* pneumonia.

‡Noted before diagnosis of *Pneumocystis carinii* pneumonia.

§Center for Disease Control classification at time of presentation of respiratory distress.¹⁴

Table 2.—Age at Diagnosis of *Pneumocystis carinii* Pneumonia and Absolute CD4 Count

Source, y	Age <12 mo CD4 Count, $\times 10^9/L$				Age >12 mo CD4 Count, $\times 10^9/L$			
	No.	<.20	200-1.00	>1.00	No.	<.200	.200-300	>.300
Present study	10	0	5	5	3	2	1	0
Leibovitz et al, ¹³ 1990	15	7	2	6	6	6	0	0
Total	25	7 (28%)	7 (28%)	11 (44%)	9	8	1	0

higher than $0.7 \times 10^9/L$, three had a CD4-CD8 ratio higher than 1.0, and seven had a CD4-CD8 ratio lower than 1.0. Five children had IgG values of less than 3.0 g/L. Twelve children, including nine of 10 younger than 12 months, had signs or symptoms of HIV infection prior to presentation with PCP (Table 1).

COMMENT

Reliance on adult values of CD4 counts to predict risk of PCP would have caused us to miss all of the 10 infants with PCP younger than 1 year; these infants had CD4 counts in excess of $0.25 \times 10^9/L$. Seventeen of the 18 patients described by Bernstein et al¹⁰ had previous CD4 counts measured. Nine (50%) of these patients had CD4 counts greater than $0.6 \times 10^9/L$. Unfortunately, the CD4 counts were not stratified by age.

Leibovitz et al¹³ recently described 22 HIV-infected children who developed PCP. Fifteen were younger than 12 months at the time of PCP diagnosis. Combining the patients in their study and ours, all nine patients older than age 12 months with available CD4 counts had absolute CD4 counts lower than $0.27 \times 10^9/L$ (Table 2). Of the 25 patients younger than 1 year, seven (28%) had absolute CD4 counts less than $0.2 \times 10^9/L$, seven (28%) had CD4 counts between $0.2 \times 10^9/L$ and $1.0 \times 10^9/L$, and 11 (44%) had CD4 counts greater than $1.0 \times 10^9/L$. Almost half of the 35 patients died during the first episode of acute PCP.

Two additional studies^{11,12} also report that high CD4 counts do not prevent the occurrence of PCP in HIV-infected children.

All these findings illustrate the lack of utility of using adult standards of CD4 counts in predicting risk of PCP in infants with HIV infection. Part of the difficulty may be the absence of normative data on T-cell counts among noninfected children. Since infants typically have relative lymphocytosis (compared with older children and adults), the criteria for a low absolute CD4 count are not yet established.

A recent abstract¹⁵ noted average CD4-CD8 ratios of 2.72 in 11 normal children younger than 18 months, with a mean absolute CD4 count of $1.8 \times 10^9/L$. A second abstract¹⁶ described a larger group of normal infants. In the 100 infants younger than age 6 months, the mean CD4-CD8 ratio was 2.3 with a mean absolute CD4 count of $3.17 \times 10^9/L$. In 70 6- to 12-month-old children, the mean ratio was 2.0 and the mean absolute CD4 count was $2.83 \times 10^9/L$. Three of our 10 infants with PCP had CD4-CD8 ratios in this range, although all had absolute CD4 counts less than $2.00 \times 10^9/L$. Larger studies are needed to stratify normal CD4 counts and CD4-CD8 ratios according to age, especially in the patients younger than 12 months.

That five of 13 children with PCP had IgG levels less than 3.0 g/L was unexpected. The vast majority of children with documented HIV infection have elevated IgG levels at the time of diagnosis.^{17,18} In normal children, IgG levels increase with age during the first year of life. The rate of increase of IgG in HIV-infected children in the first year of life has not been documented, although in one study, four of eight children had increased IgG levels by age 4 months, and six of eight by age 9 months.¹⁹ Because host

defense mechanisms for PCP are still not elucidated, the CD4 count may be only one of several relevant immunologic markers of susceptibility to PCP in infancy, and other surrogate markers should be examined. For instance, congenitally hypogammaglobulinemic infants are at risk for PCP despite normal T-cell counts.²⁰ Human immunodeficiency virus-positive infants with low IgG levels may represent a subgroup at high risk for PCP.

Half of all HIV-infected infants will have associated symptoms or diseases by age 12 months, and over 75% will be symptomatic by age 2 years.² All 18 HIV-infected patients with PCP previously reported¹⁴ experienced failure to thrive at the time of PCP diagnosis. Twelve of our 13 patients had preexisting symptoms or illnesses consistent with HIV infection before the diagnosis of PCP. In five of the 13 patients and four of the 10 infants, failure to thrive was noted before the diagnosis of PCP. Early development of HIV-related symptoms, especially the failure to thrive, may serve as a marker for infants at high risk for PCP.

Prompt identification and assessment of infants at risk for HIV infection is important because PCP may occur as early as the second month of life. Since only 30% to 40% of HIV antibody-positive newborns are actually infected, optimal care would include determining each child's immune and infectious status. Infants at risk, or those already known to be HIV antibody-positive, should be referred to a pediatric HIV center with the capability to perform HIV DNA polymerase chain reaction (PCR) and blood culture testing for HIV. Infants younger than 15 months with proven HIV infection (positive PCR or HIV blood culture) should receive prophylaxis. Because the rate of false-negative HIV cultures and PCR in childhood is not well established, infants younger than 12 months with negative results but evidence of immune dysfunction (abnormal IgG levels or CD4 counts), or compatible symptoms (failure to thrive, adenopathy, and hepatosplenomegaly), should be considered for prophylaxis. When direct HIV testing is unavailable, or the results are pending, it would be prudent to begin prophylaxis for HIV antibody-positive infants through age 12 to 15 months.

Data from this study and others suggest that an absolute CD4 count less than $0.3 \times 10^9/L$ is helpful in predicting risk of PCP in children older than 12 months, and these children should receive prophylaxis. Low IgG levels may serve as an additional marker for increased risk of PCP.

Trimethoprim/sulfamethoxazole provides relatively inexpensive and effective prophylaxis. Unfortunately, 20% to 40% of HIV-infected adults treated with trimethoprim/sulfamethoxazole develop allergic reactions.^{21,22} Of the last 15 HIV-positive children at our center who started receiving trimethoprim/sulfamethoxazole, seven developed allergic reactions requiring discontinuation of the medication (one case of erythema multiforme, two cases of acute anaphylactic reaction, and four cases of recurrent severe urticarial rashes). The use of aerosolized pentamidine for HIV-infected children allergic to trimethoprim/sulfamethoxazole is currently under investigation.

Further research needs to be devoted toward establishing normative T-cell subset data in infants. In addition, the effectiveness of alternative therapies for PCP prophylaxis in HIV-infected children remains to be determined.

I am grateful to S. Plotkin, S. Douglas, and W. Schwartz for their editorial assistance.

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Measurement of Serum Granulocyte Colony-Stimulating Factor in a Patient With Congenital Agranulocytosis (Kostmann's Syndrome)

Lewis Glasser, MD; Burris R. Duncan, MD; James J. Corrigan, Jr, MD

● A 12-month-old boy with Kostmann's syndrome was admitted with cavitary pulmonary disease. He had also had bacterial conjunctivitis, periorbital cellulitis, pneumonitis, and otitis media since the age of 10 days. His umbilical cord had not fallen off until he was 3 weeks old. Neutropenia was diagnosed at 4 weeks of age. Antineutrophil antibody studies were negative. A bone marrow aspirate showed granulocytic hypoplasia and a maturation arrest at the promyelocyte stage. Hematopoietic cell culture showed normal numbers of colony-forming units—granulocyte macrophage. Serum granulocyte-macrophage colony-stimulating factor level, was 0.24 ng/mL (normal, >0.05 ng/mL). Serum granulocyte colony-stimulating factor levels, measured by enzyme immunoassay, were undetectable. The patient was successfully treated with filgrastim (granulocyte colony-stimulating factor), with an increase in the absolute neutrophil count to $10.0 \times 10^9/L$. Thus, our case of Kostmann's syndrome appears to represent a defect in regulation or production of granulocyte colony-stimulating factor.

(AJDC. 1991;145:925-928)

Granulocyte colony-stimulating factor (G-CSF) is a recently discovered hematopoietic growth factor, and our understanding of its role in normal physiology and disease is beginning to emerge. It is primarily a neutrophilopoietin,¹ important in the regulation of granulopoiesis. It now appears evident that a defect in its production or regulation causes Kostmann's syndrome,² a congenital neutropenia that not only has benefited from G-CSF therapy³ but is an experiment of nature that provides a rare opportunity to study the homeostatic mechanisms involved in granulopoiesis. In this report, we describe the application of measuring the serum G-CSF level to the pathogenesis, diagnosis, and subsequent successful treatment of a patient with congenital agranulocytosis (Kostmann's syndrome).

PATIENT REPORT

A 3830-g boy was the product of a full-term pregnancy. He was born to a 30-year-old, gravida 5, para 3, abortus 1 mother. His mother stated that his umbilical cord did not fall off until he was 3 weeks old. At 10 days of life, he had *Chlamydia* conjunctivitis that was treated with erythromycin. At 4 weeks he had periorbital cellulitis and was found to have severe neutropenia. *Pseudomonas* grew from a culture from his conjunctivas, and he was treated for 10 days with intravenous antibiotics. He subsequently developed persistent otitis media requiring multiple courses of antibiotics, without benefit.

At 12 months of age, he developed cough and fever. A chest roentgenogram showed right-upper-lobe consolidation with cavitary lesions, and he was placed on a regimen of intravenous antibiotics. His weight and length had decreased from the 50th percentile at 4 weeks of age to below the fifth percentile at 12 months. Laboratory studies at 4 weeks of age had showed a normal hemoglobin level (113 g/L) that progressively decreased throughout his illness to a low value of 76 g/L before filgrastim (G-CSF) therapy. Platelet counts were consistently elevated at 362 to $936 \times 10^9/L$. Leukocyte counts before filgrastim therapy were as follows: white blood cells, 4.6 to $12.3 \times 10^9/L$; neutrophils, 0 to $0.32 \times 10^9/L$; eosinophils, 0 to $0.592 \times 10^9/L$; basophils, 0 to $0.327 \times 10^9/L$; monocytes, 1.0 to $5.5 \times 10^9/L$; and lymphocytes, 3.5 to $9.1 \times 10^9/L$.

After informed consent was obtained, treatment with filgrastim (Neupogen, Amgen Inc, Thousand Oaks, Calif) therapy ($6 \mu\text{g/kg}$ twice daily subcutaneously) was started at the age of 12 months for treatment of pneumonitis. Absolute neutrophil counts exceeded $5.0 \times 10^9/L$. The right-upper-lobe cavitation gradually cleared. The patient was placed on a regimen of maintenance filgrastim therapy; however, absolute neutrophil counts were consistently less than $1.0 \times 10^9/L$. During the next 7 months, he continued to have patchy parenchymal densities. At 18 months of age, he was readmitted for evaluation of chronic pulmonary changes and failure to thrive. Episodes of obstructive apnea prompted a tonsillectomy and adenoidectomy. Cultures of bronchoalveolar washings yielded cytomegalovirus. Increasing the dose of filgrastim to $12 \mu\text{g/kg}$ twice daily increased the absolute neutrophil count to $3.0 \times 10^9/L$. In the hospital he was also given nasogastric feedings of a high-energy formula. The patient's condition responded, and he showed significant clinical improvement.

MATERIALS AND METHODS

Neutrophil Antibody Assays

The indirect immunofluorescence and neutrophil agglutination tests were done as described by Lalezari and Pryce.⁴

Accepted for publication February 11, 1991.

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Presented in part at the annual meeting of the American Society of Hematology, Boston, Mass, December 3, 1990.

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Clonogenic Assays for Bone Marrow Progenitor Cells

These assays were done as previously described.⁵⁻⁷ Bone marrow light density cells were separated by density gradient centrifugation using Ficoll-Hypaque (specific gravity 1.077 g/mL). Erythrocytes were removed by hypotonic lysis. For the colony-forming unit-granulocyte macrophage assay, 1×10^5 cells were plated in 0.3% semisolid agar containing recombinant human GM-CSF. Burst-forming units-erythroid were cultured in 1.5% methylcellulose containing Iscove's modified Dulbecco's medium, 5% phytohemagglutinin-leukocyte-conditioned medium, 30% fetal bovine serum, 10^{-4} mol/L 2-mercaptoethanol, and 2 units of erythropoietin. Each plate was seeded with 5×10^4 cells. Cultures were done in quadruplicate. Plates were cultured at 37°C, in 5% carbon dioxide with humidity. Colonies (>40 cells) were counted at 14 days by means of an inverted microscope.

Serum G-CSF and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Assays

Serum G-CSF was measured by enzyme immunoassay (Amgen Inc, Boulder, Colo).^{8,9} The method uses microtiter wells coated with a rabbit polyclonal anti-G-CSF antibody. After overnight incubation, monoclonal anti-G-CSF conjugated with horseradish peroxidase was added to the wells and incubated at 37°C for 2 hours. Substrate (tetramethylbenzidine) was added, and the chromogen was read at an absorbance of 450 nm. The level of sensitivity of this assay is 50 pg/mL.

Serum samples were tested for GM-CSF (Immunex, Seattle, Wash) by means of the GM-CSF human bone marrow assay.¹⁰ Test serum samples were titered through a duplicate series of threefold dilutions. Human bone marrow cells were added to wells containing the test serum. Plates were incubated at 37°C in 10% carbon dioxide for 4 days. Tritiated thymidine was added, and plates were incubated for 4 hours. The well contents were harvested, and radioactivity was measured on a beta counter.

RESULTS

Blood Counts

Before treatment, absolute neutrophil counts ranged from 0 to $0.32 \times 10^9/L$. Most counts were $0 \times 10^9/L$, and the highest count occurred when the patient had a severe cavity pulmonary infection. After filgrastim treatment, a consistent increase in the absolute neutrophil count occurred on the 8th day (Fig 1). There was an absolute increase in numbers of band and segmented neutrophils; the neutrophils had toxic granules and Dohle bodies. Monocytosis was present, with counts ranging from 1.0 to $5.5 \times 10^9/L$, and persisted after filgrastim treatment, with counts ranging from 1.6 to $8.6 \times 10^9/L$. Before filgrastim therapy, eosinophils were seen in the blood despite severe neutropenia. After therapy, the eosinophil count did not increase significantly, ranging from 0% to 6% (0 to $0.5 \times 10^9/L$) during the first 30 days.

Bone Marrow Morphologic Characteristics

Bone marrow studies were done at the ages of 7 months (before filgrastim therapy) and approximately 13 months (23 days after filgrastim therapy). Informed consent was obtained. Before G-CSF therapy, the granulocytic series showed myeloblasts and promyelocytes but an absence of neutrophils. Eosinophils and basophils were normally present. A reactive plasmacytosis was present, presumably a reflection of chronic infections. The myeloid-erythroid ratio was markedly decreased to 0.5. Cellularity was normal. After filgrastim therapy, neutrophilic differentiation was seen, and the myeloid-erythroid ratio significantly increased to 1.1. A comparison between pretreatment and posttreatment marrow findings is shown in the Table.

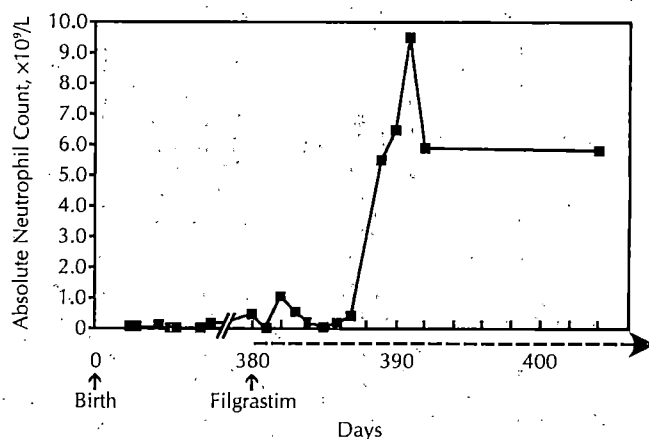


Fig 1.—Absolute neutrophil counts before and after treatment with filgrastim (granulocyte colony-stimulating factor). The dose given was 6 $\mu\text{g/kg}$ subcutaneously twice daily.

Bone Marrow Differential Counts Before and After Filgrastim (Granulocyte Colony-Stimulating Factor) Therapy

	Count, %	
	Before Therapy	After Therapy
Myeloblasts	4	2
Promyelocytes	5	7
Neutrophils		
Myelocytes	0	3
Metamyelocytes	0	3
Bands	0	9
Segmented	0	3
Eosinophils		
Myelocytes	2	1
Metamyelocytes	1	2
Bands	1	2
Segmented	2	2
Basophils	0.5	0.6
Monocytes	20	5
Pronormoblasts	1	3
Normoblasts		
Basophilic	2	2
Polychromatic	21	19
Orthochromatic	8	8
Lymphocytes	24	23
Plasma cells	6	3

Neutrophil Antibodies

Serum samples from the infant and mother were analyzed. The sample from the infant was obtained at 6 weeks of age. Results of the indirect immunofluorescence (against neutrophils from three normal donors) and neutrophil agglutination (against neutrophils from 10 donors) tests were negative.

Serum G-CSF and GM-CSF Levels

Serum samples were obtained at 8 months of age. No G-CSF was detected in the serum of the patient or four pediatric controls (7 to 35 months old). The GM-CSF level was 0.24 ng/mL (six replicates) by the bioassay (normal, >0.05 ng/mL).

Colony-Forming Unit-Granulocyte Macrophage and Burst-Forming Unit-Erythroid Assays

The bone marrow (before treatment) at 7 months of age showed normal progenitors, with 50 colony-forming units-granulocyte macrophage per 10^5 cells and 46 burst-forming units-erythroid per 10^5 cells.

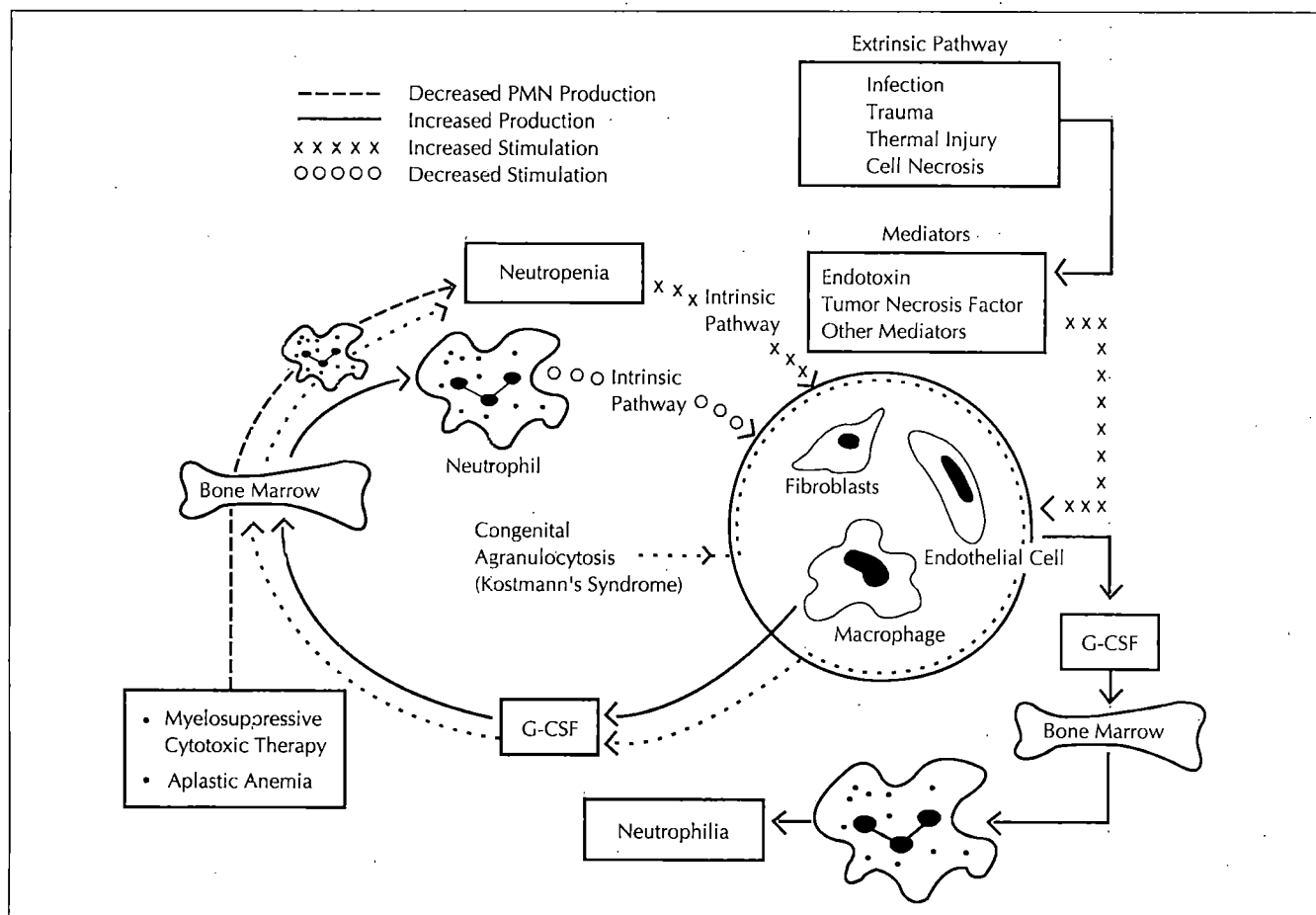


Fig 2.—Hypothetical model of the regulatory mechanisms controlling neutrophil (PMN) granulopoiesis. An intrinsic circuit is postulated that is responsible for normal neutrophil homeostasis. Low numbers of neutrophils increase the stimulation for granulocyte colony-stimulating factor (G-CSF) production; as neutrophils are produced, the stimulus for G-CSF production decreases. In disease, myelosuppressive chemotherapy and aplastic anemia are associated with low absolute neutrophil counts, stimulating the production of G-CSF from macrophages, fibroblasts, and endothelial cells. In congenital agranulocytosis (Kostmann's syndrome) there is a primary defect in the production or regulation of G-CSF, causing a low absolute neutrophil count. An extrinsic pathway also exists that bypasses the intrinsic feedback loop. In this pathway, infection, injury, or cell necrosis results in the increased production of mediators that stimulate producer cells to increase G-CSF production, promoting granulopoiesis and neutrophilia.

COMMENT

Neutropenias are caused by underproduction, excessive destruction, or increased utilization. Underproduction can be caused by cytotoxic drugs, irradiation, neoplastic infiltration of the bone marrow, nutritional deficits, or stem cell failure. Recently, hematopoietic growth factors have been identified and characterized,¹¹ and it is becoming clear that abnormal regulation or production of growth factors also causes underproduction of neutrophils. The regulation of neutrophil production is not fully understood; however, it is established that G-CSF is primarily a neutrophilopoietin without much effect on other granulocytes.^{1,3,12} In our patient, the presence of eosinophils in the bone marrow and blood with an absolute neutrophil count of $0 \times 10^9/L$ and the absence of eosinophilia during filgrastim therapy is similar to the observations of others, providing strong evidence that separate regulatory mechanisms control each of these cell types even though both are granulocytes. Thus, the term G-CSF is a misnomer, and *neutrophil-colony-stimulating factor* would be more appropriate. In contrast, GM-CSF is known to stimulate the production of eosinophils as well as neutrophils and monocytes. In addition to GM-CSF, the humoral regulation of eosinophils is influenced by interleukin 3 and interleukin 5.¹³

A proposed hypothetical model for the control and regulation of neutrophil granulopoiesis is shown in Fig 2. Granulocyte colony-stimulating factor is produced by monocytes, fibroblasts, and endothelial cells.¹¹ There is evidence suggesting that both intrinsic and extrinsic pathways may control secretion of G-CSF from producer cells. Although evidence of a feedback mechanism controlling G-CSF production was previously lacking, a recent study supports the hypothesis that an intrinsic feedback system regulates neutrophil homeostasis.¹ In aplastic anemia, there was an inverse relationship between the absolute neutrophil count and G-CSF levels; in cyclic neutropenia, G-CSF levels increased during the neutropenic phase and decreased during the neutrophilic phase; during myelosuppressive therapy, G-CSF levels rose as the absolute neutrophil count decreased.¹ On the other hand, an extrinsic pathway appears to be primarily involved in the host's response to infection and inflammation. In these conditions, mediators (eg, endotoxin, tumor necrosis factor) directly stimulate producer cells to secrete G-CSF.¹¹ This extrinsic circuit bypasses the intrinsic homeostatic feedback mechanism, stimulating producer cells to secrete G-CSF. Thus, the absolute neutrophil count varies directly with serum G-CSF levels in bacterial infections and lung cancer.¹

Deciphering the variables involved in neutrophil granulopoiesis is dependent on a sensitive and reliable assay for serum G-CSF. Biologic assays are nonspecific, and immunoassays still lack sufficient sensitivity to detect serum levels in normal individuals. A previous report indicated that G-CSF was not detectable or within the normal range in patients with congenital agranulocytosis. Unfortunately, the level of sensitivity of the assay was 0.8 ng/mL, too high for critical evaluation.¹² Recent modifications have improved the assay, and the present limit of sensitivity is 30 or 50 pg/mL.⁹ The assay is capable of detecting G-CSF in only 12% of healthy adults; the highest reported level in healthy adults was 163 pg/mL.¹ Levels of G-CSF were undetectable (<50 pg/mL) in four normal infants, 7 to 35 months of age, in our study.

The inappropriately low serum G-CSF level in our patient with congenital agranulocytosis is consistent with a defect in regulation or production, since G-CSF levels are typically elevated in other neutropenic states.¹ There are several possible explanations for the failure of G-CSF regulation or production. These include an abnormal or deleted gene on chromosome 17 with an inability of the cell to synthesize G-CSF, inability to synthesize a normal functional molecule of G-CSF, failure to synthesize normal amounts of G-CSF analogous to thalassemia, abnormal producer cell receptors that do not recognize cytokines functioning as mediators in either the intrinsic or extrinsic pathways, or target cells with decreased responsiveness to G-CSF. The last is less likely, since congenital agranulocytosis responds to exogenous recombinant human G-CSF. More than one cause may be operative in cases of congenital agranulocytosis.

In our case of congenital neutropenia, GM-CSF levels were difficult to interpret. Monocytosis was present throughout the patient's course, suggesting normal GM-CSF production. Serum GM-CSF was normal by the bioassay; however, the assay is nonspecific and also detects G-CSF, interleukin 3, interleukin 4, and interleukin 7. Immunologic methods for measuring serum GM-CSF lack sensitivity in the normal range. It is probable that when the sensitivity of the more specific immunoassay method is improved, GM-CSF levels of body fluids will be found to be either normal or increased in Kostmann's syndrome.

The causes of isolated congenital neutropenia include immune neonatal neutropenia, congenital agranulocytosis (Kostmann's syndrome), cyclic neutropenia, and chronic idiopathic neutropenia. In immune neonatal neutropenia, the neutropenia is secondary to transplacental transfer of antibodies from mother to fetus. Serum G-CSF levels have not been reported. In Kostmann's syndrome, progenitor cells are present, as shown by normal growth of colony-forming units-granulocyte macrophage in our patient and as reported by others¹⁴; in our patient, the serum G-CSF level was inappropriately low. Pietsch et al¹⁵ showed that monocytes from patients with Kostmann's syndrome produce G-CSF. This suggests a defect in regulation but does not exclude a primary defect in production. In our patient, absolute neutrophil counts were low in both the infected and noninfected state. The highest neutrophil count was obtained when the patient had a severe cavitary pulmonary infection, perhaps indirectly suggesting an abortive response to inflammatory stimuli. Serum G-CSF levels were not measured at this time. In contrast to Kostmann's syndrome, in cyclic neutropenia there is a defect in the regulation of granulopoiesis, and

serum G-CSF levels are high during the neutropenic phase and low during the neutrophilic phase.¹ Chronic idiopathic neutropenia most likely represents a heterogeneous group of patients. Serum G-CSF levels have not been reported in these patients but would be of interest and could potentially elucidate the various causes and aid in the classification of this diverse group.

CONCLUSION

The cause of Kostmann's syndrome is not known. Our patient had severe neutropenia with an inappropriately low serum G-CSF level, suggesting that the cause of this disorder is a defect in either the regulation or the production of G-CSF. The defect is isolated to G-CSF and does not involve the cytokine GM-CSF.

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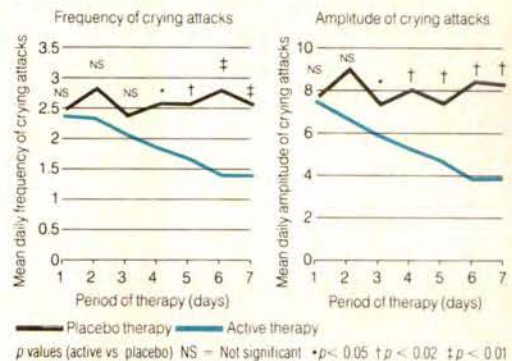
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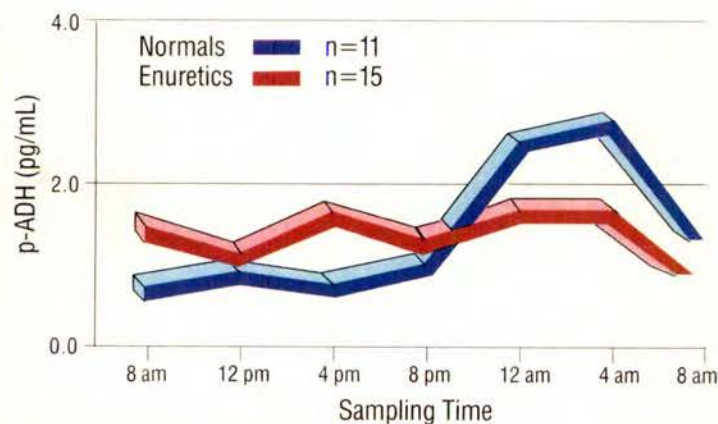
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PZ24

Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children¹

Mean diurnal variation in plasma
antidiuretic hormone (p-ADH) between
normal and enuretic children¹

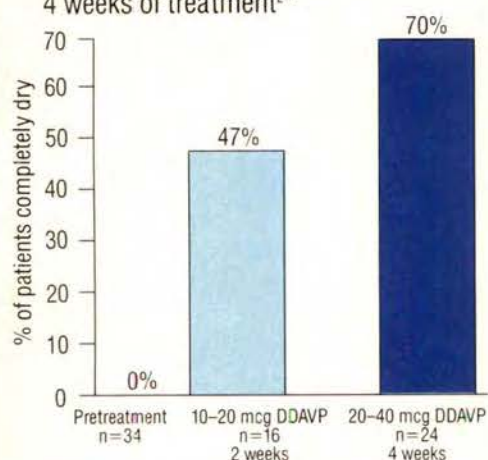


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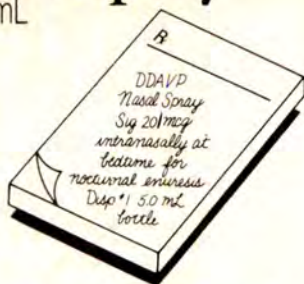
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CONTRAINDICATION: Known hypersensitivity to DDAVP.

WARNINGS: 1. For intranasal use only.
2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.
Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient monitoring.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmopressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no uterine action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleeds, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

	PLACEBO (N=59)	DDAVP 20 mcg (N=60)	DDAVP 40 mcg (N=61)
ADVERSE REACTION	%	%	%
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	3
Dizziness	0	0	0
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	0	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP.

An oral LD₅₀ has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

HOW SUPPLIED: A 5 mL bottle with spray pump delivering 50 doses of 10 mcg (NDC 0075-2450-02). Keep refrigerated at 36°-46°F (2°-8°C). When traveling, product will maintain stability for up to 3 weeks when stored at room temperature, 72°F (22°C).

See product circular for full prescribing information.

Rev 6/89

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Use of Infant Walkers

Board of Trustees

● Infant walkers are used by many parents because of the convenience they provide in keeping children occupied. Unfortunately, parents may develop a false sense of security that leads to diminished vigilance over the safety of their infant. Although most injuries that result from walkers are minor, serious trauma from head injuries, lacerations, and burns does occur occasionally. The American Medical Association recommends that physicians counsel parents on the risk of injury that can occur from the use of infant walkers and inform parents that these devices do not either promote bipedal ambulation or offer a substitute for careful parental supervision.

(AJDC. 1991;145:933-934)

Concern for the safety of infants who use walkers first surfaced in the early 1970s when the federal government developed standards under the Federal Hazardous Substance Act (1971) that regulated the construction of walkers and jumpers to prevent the crushing of fingers or toes. The Consumer Product Safety Commission, in a 1974 study involving review of visits to 176 emergency departments and personal interviews, found that 3700 children had received treatment for trauma resulting from use of infant walkers.^{1,2} Most of these were infants under age 2 years. From a follow-up survey in 1980, the Consumer Product Safety Commission reported that 24 000 infants had sustained an injury related to use of walkers resulting in 8600 emergency department visits; 54% of these involved trauma from falling down stairs.³ Although the results of other studies have confirmed the initial concerns, the samples investigated have been relatively small and there have been no efforts to compare the rates and types of injuries between infants who use walkers and those who do not.⁴⁻⁸ With these limitations in mind, the epidemiology of walker injuries may be summarized as follows:

1. Between 70% and 80% of infants will use a walker, mostly between ages 5 and 12 months; twice as many boys use walkers as girls.
2. Of infants who use walkers, 30% to 40% will have an accident.
3. Most walker accidents are minor and relatively few result in contact with a physician.

4. The most common types of accident involve falling down stairs, tipping over, and finger entrapment. Other injuries result from infants pulling objects down onto themselves.

5. Of infants seen in emergency departments for a walker injury, almost all serious trauma results from falling down stairs. Over 90% of all stairwell injuries among infants less than 12 months of age are related to use of walkers. Closed head injury is the most common serious walker injury, followed by fractures (skull, arm, clavicle) and other trauma, such as burns, dental injuries, and lacerations.

6. Of infants with serious injury, about one third stop walker use immediately, one third stop use within 2 months (usually because infants begin walking on their own), and one third are still using a walker 2 months after the injury.

7. Most walker injuries occur in the home with one or both parents present. Of injuries involving stairs, about half occur in houses with stairwell gates.

8. Although the occurrence of trauma is unrelated to the age at first use, number of siblings, and parents' occupations, it is related to the amount of time spent in the walker. Fewer than 30% who spend less than 2 hours a day in a walker suffer a nonserious fall, compared with approximately 55% of infants who spend more than 2 hours per day in a walker.

9. The types of walkers involved in serious injury are fairly evenly divided between the X-frame, in which the steel support bars form an X, and the circular frame, in which the support bars go up in a straight vertical pattern to reach the upper tray.

An estimated one million infant walkers are sold each year.³ The most common reason given by parents is to keep the infant quiet, occupied, and happy. Although many parents use these devices to stimulate ambulation, there is no supportive evidence that walkers help babies learn to walk sooner.⁹ Because the type of leg movement stimulated by walkers is different from that found with nonassisted locomotion, there is some concern that they may actually impede ambulation among infants with spastic cerebral palsy.¹⁰ No studies, however, have confirmed the concern that use of walkers adversely affects development of either apparently normal infants or those who have or who are at high risk for neurologic delay in ambulation.

Walkers are popular among some parents because of the convenience they provide in keeping children occupied.

Accepted for publication January 3, 1991.

From the Board of Trustees, American Medical Association, Chicago, Ill.

Reprint requests to 515 N State St, Chicago, IL 60610 (Jerrold Loeb, PhD).

Unfortunately, this convenience creates, among some parents, a false sense of security resulting in diminished vigilance over the safety of the infant. Injuries among infants who use walkers are common, but usually minor. Although relatively rare, such serious trauma as head injuries, lacerations, and burns do occur occasionally. Parents also have a mistaken belief that walkers promote bipedal ambulation.

However, because the use of infant walkers provides some degree of danger to unsupervised infants, the American Medical Association recommends that "physicians counsel parents on the risk of injury that can occur from the use of infant walkers and inform parents that these devices do not either promote bipedal ambulation or offer a substitute for careful parental supervision."

This report was passed by the AMA House of Delegates in June 1990.

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G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Overdosage: Signs and Symptoms: Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2 1/2-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2 1/2-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

Dosage and Administration: Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: 1/2 teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

Do not exceed 6 doses during a 24-hour period. Rev. May 1987.

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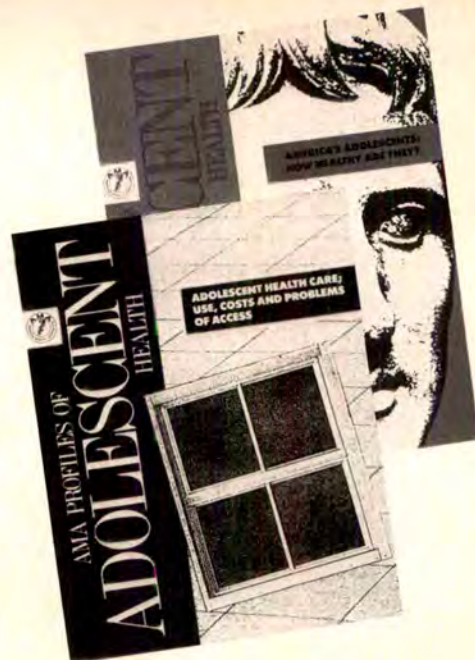
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Rice Solution and World Health Organization Solution by Gastric Infusion for High Stool Output Diarrhea

Felipe Mota-Hernández, MD, PhD; Daniel Bross-Soriano, MD; Maria L. Pérez-Ricardez, MD, PhD;
Luis Velásquez-Jones, MD, PhD

● We sought to determine the efficacy of three different types of treatment in children with acute diarrhea who, during the oral rehydration period, had high stool output (>10 mL/kg per hour). Sixty-six children, aged 1 to 18 months, with an average stool output of 22.6 mL/kg per hour were randomly distributed into three groups: group 1 received a rice flour solution, group 2 received the World Health Organization rehydration solution by gastric infusion, and group 3 continued to receive this solution orally. In all three groups, a decrease in stool output was observed, with the higher decrease observed in group 1 patients. Such a decrease facilitated rehydration of all 22 patients in group 1 (100%) in 3.3 ± 1.5 hours, 16 (73%) in group 2 in 4.3 ± 2.1 hours, and 15 (69%) in group 3 in 4.9 ± 2.0 hours. No complications were observed. These data indicate that the rice flour solution is effective in children with high stool output diarrhea.

(AJDC. 1991;145:937-940)

The use of the oral rehydration therapy (ORT) with the formula recommended by the World Health Organization (WHO)¹ has constituted a great advance for the treatment of dehydration secondary to diarrhea. A successful outcome in more than 90% of patients treated for 4 to 6 hours has been reported.^{2,3} Unfortunately, this treatment usually fails in the high stool output state and hydration by the intravenous route is usually required.³ Some authors⁴ have proposed the use of a nasogastric tube (gastric infusion) as an alternate mode of therapy. This method of delivering lower volume at a constant rate may increase intestinal absorption of water, thus circumventing the intravenous route.

It has been proposed that products of rice starch hydrolysis, such as amylose and amylopectin (which ultimately break down into glucose), amino acids (glycine), dipeptides (glycyl-glycine), and short-chain oligosaccha-

rides (<10 molecules of glucose), enhance the absorption of sodium and water through an active membrane transport mechanism at the intestinal level without presenting an unwanted osmotic charge.⁵⁻⁸ This might then account for the beneficial effect of oral rice solution on stool output during the correction of dehydration in children with liquid diarrhea.⁹⁻¹²

Our purpose was to compare the usefulness of rice flour solution with no electrolytes added (RFS) with the WHO formula administered either by the oral route (WHO) or through gastric infusion. The aim was to reduce the stool output in children in whom a high stool output was documented during the initial period of ORT.

PATIENTS AND METHODS

Sixty-six children whose ages ranged from 1 to 18 months, who presented with dehydration due to acute diarrhea of less than 17 days' duration and a persistent high stool output (>10 mL/kg per hour for 2 consecutive hours) during the oral rehydration period, were included in the trial. Stool output was calculated as the volume of feces in 1 hour divided by the patient's weight. The patients were seen between March 1988 and April 1989 at the Oral Hydration Ward of the Hospital Infantil de México "Federico Gómez, Mexico City."

Patients were excluded from the study if they had the following associated problems: acute renal failure, septicemia, meningitis, bronchopneumonia, third-degree malnutrition, persistent or progressive abdominal distention with suspicion of ileus or intestinal perforation, and those who had received gastric infusion in the preceding 12 hours or with an altered state of consciousness or in shock.

Before the children were admitted into our study and according to the routine management for dehydrated children at our hospital, all patients received ORT with the citrate WHO formula containing 90 mmol/L of sodium, 80 mmol/L of chloride, 20 mmol/L of potassium, 10 mmol/L of citrate, and 111 mmol/L of glucose.¹³ The initial dose (100 mL/kg) was calculated for a 4-hour period. If, at any point during the observation period (at 1-hour intervals), the stool output was greater than the oral ingestion, the amount of oral solution offered in the next hour was increased to the equivalent of the stool loss during the previous hour plus 10%. All patients received 50 to 100 mL/kg of oral rehydration solution with the WHO formulation, given at a rate of 25 mL/kg per hour before entering the study. Not all the patients continued to receive the WHO formula during all 4 hours of this period because the criteria for their inclusion was that they had high stool outputs during 2 consecutive hours, and this requirement was reached after 2, 3, or 4 hours.

Accepted for publication December 12, 1990.

From the Servicio de Hidratación Oral, Hospital Infantil de México, "Federico Gómez," México.

Read before the 19th International Congress of Pediatrics, Paris, France, July 28, 1989.

Reprint requests to the Servicio de Hidratación Oral, Hospital Infantil de México, "Federico Gómez," Dr Marquez No. 162, Col. Doctores, 06720 Mexico D. F., Mexico (Dr Mota-Hernández).

Table 1.—Clinical Characteristics of 66 Children With High Stool Output Diarrhea Treated With Rice Flour Solution (Group 1), World Health Organization Solution by Gastric Infusion (Group 2), or by Oral Route (Group 3)*

Characteristics	Group 1 (n=22)	Group 2 (n=22)	Group 3 (n=22)
Sex Ratio, M/F	13/9	12/10	14/8
Age, mo	8.54±3.6	8.18±3.9	10.36±5.1
Malnourished, No.	1	0	3
Evolution, h	89.7±75.6	124.9±103.2	96.9±115.9
Dehydration, %	5.9±2.5	7.2±2.6†	5.5±2.2†
Stool output, mL/kg per h	22.2±8.7	25.5±10.6	20.5±9.0

*Values are mean ± SD, unless otherwise stated.

† $P < .05$ between groups B and C.

Table 2.—Previous Stool Output and During Treatment With Rice Flour Solution (Group 1), World Health Organization Solution by Gastric Infusion (Group 2), or by Oral Route (Group 3) in 66 Children With High Stool Output Diarrhea*

Group	Outcome	No.	Stool Output	
			Previous	During Treatment
1	Success	22	22.2±8.7	4.2±1.9†
2	Success	16	23.1±7.3	5.3±2.7†
	Failure	6	31.2±7.3	12.2±3.5†
3	Success	15	18.7±4.8	5.6±1.9†
	Failure	7	24.4±11.7	19.3±8.7

*Values are mean ± SD.

† $P < .05$.

Table 3.—Rehydration Time in 53 Children With High Stool Output Diarrhea and Favorable Outcome With Rice Flour Solution (Group 1), World Health Organization Solution by Gastric Infusion (Group 2), or by Oral Route (Group 3)

Group	Rehydration	Time, h*	No.
1	3.3±1.5†	(1-6)	22
2	4.3±2.0	(1-8)	16
3	4.9±2.0†	(2-8)	15
Total	4.0±1.9	(1-8)	53

*Values are mean ± SD (range).

† $P < .05$ between groups 1 and 3.

All eligible patients with persistent high stool output during the oral rehydration period, independently of the degree of dehydration, were divided into three groups by a list of random treatment assignments¹⁴: patients in group 1 received RFS, patients in group 2 received the WHO solution via gastric infusion, and patients in group 3 (the control group) continued to receive the WHO formula orally. The RFS was prepared with 50 g of rice flour and cooked for 10 minutes in water. If necessary, water was added to complete 1 L. The RFS analysis (22 samples) showed a sodium concentration of 1.4 ± 1.0 mmol/L (mean ± SD), a potassium concentration of 2.0 ± 0.9 (mean ± SD), and an osmolality of 47.1 ± 10.3 mmol/L (mean ± SD).

In the three groups, a constant balance of fluid was measured, body weight was determined, and the evolution of the clinical signs of dehydration were recorded every hour. The patients received the same volume calculated previously. If, during any of

the observation periods, the feces excretion was greater than the amount of ingestion, the volume of solution offered the following hour was increased in the same way as before entering the study.

If, during the first 2 hours of the study, the rate of stool loss decreased by 30% or more in relation to the previous average rate output during the 2 hours before entering the study, the administration of the same solution was continued through the same route in the required volumes until a normal state of hydration, assessed separately by two physicians, was obtained. Patients were closely monitored for clinical changes. The treatment was judged to be successful if there was both clinical response with decreased stool volume and correction of dehydration within 8 hours of initiation of ORT when admitted to our service.

In patients in whom fecal output did not decrease more than 30% during the first 2 hours of the study, treatment was considered to be a failure. In those in whom hydration was not attained in less than 8 hours, treatment was also considered to be a failure independently of the decrease in fecal output. All patients in whom treatment failed were hydrated by the intravenous route.

In admitting the patients to the study, the following laboratory values were determined: sodium, potassium, and osmolality in serum and stool; serum glucose; and hemoglobin. Stool culture, investigation for rotavirus (by rotaphoresis), and assessment for ova and parasites were also performed.¹⁵ When the state of dehydration was corrected or the patients were withdrawn from the study because of treatment failure, serum sodium, potassium, and hemoglobin levels were determined.

The sample size was determined by seeking a decrease of 30% in the rate of diarrhea output to be obtained with the use of RFS or gastric infusion. The mean value previously observed in our hospital for a group of 24 infants with high stool output requiring intravenous fluids was 17.89 ± 7.04 mL/kg per hour (mean ± SD). Therefore, the expected decrease would be 6 mL (30%). The calculated sample sizes included 22 cases in each group with use of a two-tailed test¹⁶ as follows: $[2(\text{SD})^2/(\text{expected difference})^2] \times 80\%$ of weight of the expected probability ($P < .05$), or $[2(7.04)^2/(6)^2] \times 7.9 = 22$ cases in each group.

The Mann-Whitney *U* Test, Wilcoxon Matched-Pairs Signed-Rank test, and Student's paired *t* test were used for statistical analysis.¹⁷ The study was approved by the Hospital Infantil de México "Federico Gómez" Ethics Committee. Signed informed consent was obtained from the parents.

RESULTS

A summary of the characteristics of patients included in the three groups is shown in Table 1. The groups were comparable with respect to age, sex, duration of diarrheal state, and stool output volume. Except for four children with second-degree malnutrition, the patients were well nourished. The mean percentage (±SD) of dehydration, defined by the recuperation of weight observed when obtaining the state of normohydration, was $6.4\% \pm 2.7\%$, with a range from 2% to 13%; three patients in each group were severely dehydrated (>10%). There was a greater degree of dehydration in those patients in group 2, but these differences only became significant ($P < .05$) when compared with group 3, but not with group 1. In one third of the cases, the stool output was higher than 25 mL/kg per hour, distributed as follows: eight in group 1, 10 in group 2, and four in group 3.

A reduction in stool output of more than 30% was observed in all three groups since the first hour of the study. This reduction, as shown in Table 2, facilitated the rehydration of all 22 patients in group 1, 16 of 22 patients in group 2, and 15 of 22 patients in group 3. The failure rate in the patients rehydrated by gastric infusion was 27% (group 2) and 31% in the group hydrated by the oral route (group 3). Moreover, the stool output reduction was

Table 4.—Initial Laboratory Data From 66 Dehydrated Children With Diarrhea Treated With Rice Flour Solution (Group 1), World Health Organization Solution by Gastric Infusion (Group 2), or by Oral Route (Group 3)*

Examination	Total Patients (N = 66)	Group 1 (n = 22)	Group 2 (n = 22)	Group 3 (n = 22)
Stool				
Sodium, mmol/L	50.7 ± 33.9 (8-182)	41.4 ± 26.5 (8.1-75)	50.5 ± 34.4 (13.5-94)	60.4 ± 37.7 (20-182)
Potassium, mmol/L	18.8 ± 9.4 (3.5-54)	19.8 ± 10.7 (3.5-46)	19.1 ± 13.1 (7.2-54)	18.3 ± 7.1 (8-33)
Osmolarity, mosm/kg	200.6 ± 65.1 (63-387)	212.9 ± 76.2 (114-320)	214.0 ± 75.3 (63-322)	183.5 ± 51.3 (131-387)
Serum				
Glucose, mmol/L	5.6 ± 1.5 (2.8-11.1)	5.3 ± 1.3 (3.8-7.8)	5.5 ± 5.2 (2.8-8.3)	6.0 ± 1.7 (3.5-11.1)
Hemoglobin, g/L	120 ± 16 (90-164)	126 ± 18 (90-146)	116 ± 12 (98-142)	120 ± 14 (92-164)
Hemoglobin, (postt rehydration), g/L	112 ± 13 (84-135) [53]	117 ± 13 (93-135) [22]	112 ± 10 (91-131) [16]†	107 ± 14 (84-130) [15]†

*Values are mean ± SD (range) [number].

†Successful cases.

greater in those patients who were successfully rehydrated with RFS (group 1) than in patients in groups 2 and 3. During analysis of the average stool output of those patients in groups 2 and 3 in whom treatment failed, it was observed that the previous stool output was higher in group 2, showing a statistically significant difference (Table 2).

The time required to achieve hydration was shorter in the 22 patients hydrated successfully in group 1 than in the 16 patients in group 2 and in the 15 patients of group 3, with $P < .05$ between groups 1 and 3 (Table 3). In contrast, the quantity of solution required to obtain normohydration (mean ± SD) was lower in group 1 than in groups 2 and 3 (65.8 ± 36.2 , 85.0 ± 38.4 , and 93.1 ± 45.7 mL/kg, respectively), but the differences were not statistically significant. None of the patients in the study suffered a relapse, and none of those in whom treatment was considered to be successful required intravenous therapy.

No statistically significant differences were observed in the laboratory results of the three groups (Table 4). In the three groups, a nonsignificant decrease in the final concentration of serum sodium and potassium occurred when the state of normohydration was achieved (Table 5). No cases of symptomatic hyponatremia or hypokalemia were observed.

As to the causative agents, enteropathogens were identified or isolated in 25 (38%) of 66 children (Table 6). No causative agent was observed in the remaining 62% of the patients studied. No correlation was found between cause and the clinical evolution.

COMMENT

The most important finding in our study was that correction of high stool output permitted rehydration in all 22 patients treated with RFS. In contrast, in almost one third of the cases managed with WHO solution (by oral route or by gastric infusion), the high stool output persisted, thereby hindering the correction of dehydration. Previous studies of ORT^{18,19} have shown that the most frequent cause of failure was precisely the presence of a high stool output.

Table 5.—Serum Sodium and Potassium Concentrations Before and After Rehydration in 53 Dehydrated Children With Diarrhea Treated With Rice Flour Solution (Group 1), World Health Organization Solution by Gastric Infusion (Group 2), or by Oral Route (Group 3)*

Group	Serum Levels, mmol/L			
	Initial (N = 66)		Final (n = 53)	
	Sodium	Potassium	Sodium	Potassium
1	146.3 ± 6.2 (138-161)	4.2 ± 0.7 (3.5-5.9)	141.7 ± 4.5 (135-148)	3.9 ± 0.7 (2.8-5.6)
2	148.9 ± 8.2 (134-160)	4.2 ± 0.8 (3.0-6.5)	145.4 ± 7.2 (141-158)	4.1 ± 0.4 (3.4-4.5)
3	145.8 ± 6.9 (132-170)	4.0 ± 0.9 (2.4-6.3)	141.2 ± 6.0 (127-143)	3.6 ± 0.9 (2.1-4.6)

*Values are mean ± SD (range).

Table 6.—Causes of Diarrhea in 25 Dehydrated Children Treated With Rice Flour Solution (Group 1), World Health Organization Solution by Gastric Infusion (Group 2), or by Oral Route (Group 3)*

Cause	Group 1	Group 2	Group 3	Total
Rotavirus	6	2	3	11
<i>Escherichia coli</i>	1	2	...	3
<i>Shigella flexneri</i>	1	1	1	3
<i>Campylobacter</i>	1	1
<i>Candida albicans</i>	1	1
<i>Klebsiella species</i>	...	1	...	1
<i>Pseudomonas</i>	...	1	...	1
<i>Cryptosporidium</i>	1	1
<i>Giardia lamblia</i>	1	1	1	3
Total	11	8	6	25 (38%)

It has been suggested that the osmolarity of a solution is inversely related to its intestinal absorption and that it enhances active intestinal secretion that in turn increases stool output.²⁰ Based on this knowledge, no electrolytes

were added to the RFS in our study. The widespread use of RFS without electrolytes for the management of all cases of dehydration secondary to diarrhea has some inconveniences, such as fast fermentation and the hardware needed to cook the rice before its administration,^{18,21,22} but the most important drawback is the risk of hyponatremia. To explain why hyponatremia was not induced in our patients, we assume that the initial treatment with the WHO solution for 2 to 4 hours may have provided sufficient electrolytes to maintain their normal serum levels during and after the RFS treatment period. Furthermore, at the beginning of the study, most of the patients included had an improved state of hydration.

An advantage of RFS over the WHO formula is that lower amounts of starch are required to correct dehydration and diminish the rate of diarrhea.^{9,11} This advantage was also demonstrated in our study, even in patients with severe dehydration. Our study is the first we know of in which RFS without electrolytes has been used specifically for the treatment of children with persistent high stool output diarrhea and provides evidence that this condition may be an indication for RFS.

Whether the use of RFS powder solution plus electrolytes is equally effective in diminishing the stool output in children with persistent high output diarrhea remains to be clarified. Also left to be elucidated is the usefulness of RFS in children who, in addition to dehydration and high stool output rate, have third-degree malnutrition. In these patients, a subnormal intestinal hydrolytic process may interfere with rice starch digestion, as has been shown in children younger than 4 months.⁹ In our study, however, a 3-month-old infant was adequately hydrated with RFS during a 2-hour period. Finally, we cannot determine the value of RFS in patients with chronic diarrhea, because they were not included in our study.

In the gastric infusion group, the six treatment failures occurred in those patients who had the highest stool output, and the decreased stool output in the 16 patients in whom treatment was successful was similar to that observed in the RFS group. One could speculate, then, that the efficiency of the RFS could be similar to that of the WHO formula administered by gastric infusion, except in those cases with the highest stool output. The success achieved in some patients who continued to receive the WHO formula by the oral route suggests that in some patients with high stool output, the administration of oral rehydration salts can diminish the stool output and correct the dehydration if one waits the required time to achieve it.

Although no cases of hyponatremia or hypokalemia were observed, and despite the good results obtained with the use of RFS in our study, we cannot dismiss the possibility that in patients with severe depletion of these cations, the prolonged administration of electrolyte-free RFS could worsen these complications. Its indiscriminate or prolonged use—mainly in malnourished children—should be avoided.

We conclude that RFS administered orally for short periods and after ORT may be useful in the treatment of well-nourished children with acute high stool output diarrhea and dehydration.

We thank Drs E. Aguilar-Parada, PhD, J. I. Santos, PhD, J. J. Urrutia, PhD, and M. Merson, PhD, for reading and revising the manuscript and Laura Leon for manuscript transcription. We also thank the Hospital Infantil de México "Federico Gómez" pharmacy, lab-

oratory, resident physicians and interns, and Oral Hydration Department nursing staff for their invaluable support and cooperation in conducting our study.

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Low Serum Calcium and High Parathyroid Hormone Levels in Neonates Fed 'Humanized' Cow's Milk-Based Formula

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• We previously suggested that "late" neonatal hypocalcemia is related to a low calcium-phosphorus ratio of current cow's milk-based formula compared with human milk. However, there are no longitudinal studies of ionized calcium and parathyroid hormone concentrations in neonates receiving formulas with varying Ca/P ratios. Sixty-nine term neonates were studied through 2 weeks of age, and formula-fed neonates were randomized at birth to receive formula with molar ratios of 0.9, 1.2, or 1.4. Serum phosphate concentrations on days 2 and 6 of age were higher, and ionized calcium levels lower on days 6 and 14, in formula-fed vs human milk-fed neonates. Serum intact parathyroid hormone level increased between days 2 and 6 in formula-fed neonates compared with a decrease in human milk-fed neonates. Serum parathyroid hormone level on day 6 correlated with phosphorus intake among formula-fed neonates. No differences were noted in serum mineral or hormone levels among formula-fed groups. We speculate that the lowering of serum ionized calcium concentrations in neonates fed a modern "humanized" cow's milk formula may be a factor in late neonatal hypocalcemia.

(AJDC. 1991;145:941-945)

Standard cow's milk-based infant formulas have a calcium-phosphorus molar ratio of approximately 1.0. Although it is generally assumed that these formulas are sufficiently "humanized" with respect to calcium and phosphorus content, we have observed that neonates fed these formulas occasionally suffer hypocalcemic convulsions and apparent secondary hyperparathyroidism within the first weeks of age.¹ Hypocalcemia in neonates presumably is related to the higher phosphate load of

these formulas when compared with human milk (Ca/P molar ratio, approximately 1.6), and a more optimal Ca/P ratio theoretically might be between 1.2 and 1.6, closer to that of human milk.

There are no longitudinal studies of serum calcium, phosphorus, and parathyroid hormone (PTH) changes in normal neonates fed formulas with varying Ca/P ratios compared with neonates fed human milk. We undertook such a study to determine the effect of cow's milk-based formulas containing varying Ca/P ratios (0.9, 1.2, and 1.4) on indicators of calcium and parathyroid status during the first 2 weeks of age. These results were compared with those obtained from neonates receiving human milk.

The major hypotheses tested were that during the neonatal period, (1) serum calcium concentrations would be lower, and serum phosphorus and PTH concentrations higher, in neonates fed cow's milk-based formula compared with neonates fed human milk; and (2) neonates fed formula with a higher Ca/P ratio than that in standard infant formula would have calcium indices more similar to those in neonates fed human milk.

SUBJECTS AND METHODS

A total of 69 term, white neonates were studied from birth and completed the 14-day study period. Four parallel groups were studied longitudinally: a group of 20 neonates fed human milk (approximate concentrations of calcium and phosphate, 8.2 and 4.8 mmol/L; Ca/P molar ratio, 1.6; Ca/P weight ratio, 2.0) and three groups of neonates fed cow's milk-based formula identical in composition except for the amount and ratio of calcium and phosphorus. Commercially available formula (Similac, Ross Laboratories, Columbus, Ohio) was used as the low Ca/P ratio formula; the two additional formulas were developed by Ross Laboratories, Columbus, Ohio, and contained different amounts of calcium and phosphorus. The measured concentrations of the lots used for the three formula-fed groups were as follows: Ca/P molar ratio, 0.9 (calcium, 14.2 mmol/L; phosphate, 15.3 mmol/L; Ca/P weight ratio, 1.2; n = 16); Ca/P molar ratio, 1.2 (calcium, 17.5 mmol/L; phosphate, 14.6 mmol/L; Ca/P weight ratio, 1.5; n = 17); and Ca/P molar ratio, 1.4 (calcium, 20.3 mmol/L; phosphate, 14.9 mmol/L; Ca/P weight ratio, 1.7; n = 15).

Investigators and mothers of the formula-fed neonates were "blinded" to the formula that was being used. All neonates were above the 10th percentile in birth weight and birth length and had 1- and 5-minute Apgar scores of 7 or greater and 8 or greater.

Accepted for publication April 18, 1991.

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Presented in part at the Society for Pediatric Research Annual Meeting, Washington, DC, May 5, 1988.

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Serum Mineral and PTH Concentrations Over First 2 weeks of Age by Type of Feeding*

	Human Milk	Formula		
		0.9 Ca/P	1.2 Ca/P	1.4 Ca/P
Calcium, mmol/L				
Day 2	2.30 ± 0.18 (25)	2.32 ± 0.14 (12)	2.62 ± 0.14 (17)	2.42 ± 0.12 (15)
Day 6	2.59 ± 0.16 (20)	2.52 ± 0.23 (16)	2.42 ± 0.25 (12)	2.54 ± 0.15 (11)
Day 14	2.67 ± 0.15 (15)	2.62 ± 0.10 (13)	2.64 ± 0.16 (16)	2.62 ± 0.15 (14)
Ionized calcium, mmol/L				
Day 2	1.25 ± 0.08 (26)	1.23 ± 0.08 (15)	1.25 ± 0.09 (18)	1.28 ± 0.06 (16)
Day 6	1.44 ± 0.10 (18)	1.34 ± 0.04 (11)	1.28 ± 0.08 (12)	1.34 ± 0.05 (15)
Day 14	1.46 ± 0.06 (17)	1.40 ± 0.06 (14)	1.39 ± 0.04 (14)	1.43 ± 0.03 (13)
Phosphate, mmol/L				
Day 2	1.71 ± 0.40 (25)	2.09 ± 0.11 (11)	2.13 ± 0.24 (17)	1.94 ± 0.42 (16)
Day 6	1.61 ± 0.29 (19)	2.32 ± 0.36 (14)	2.45 ± 0.21 (12)	2.32 ± 0.36 (12)
Day 14	1.94 ± 0.29 (15)	2.13 ± 0.27 (14)	2.29 ± 0.55 (16)	2.00 ± 0.38 (13)
Intact PTH, μ L Eq/mL				
Day 2	84 ± 34 (18)	70 ± 52 (6)	53 ± 20 (9)	86 ± 55 (12)
Day 6	50 ± 19 (14)	96 ± 72 (8)	70 ± 37 (7)	87 ± 69 (9)
Day 14	54 ± 21 (12)	63 ± 35 (10)	73 ± 17 (8)	65 ± 22 (6)

*PTH indicates parathyroid hormone. Molar ratios of calcium to phosphorus are given for three formulas given formula-fed groups. Values are mean \pm SD (number of subjects).

None of the neonates had evidence of cardiac, respiratory, gastrointestinal, or other systemic disease. There were no significant maternal medical histories that could affect fetal growth, such as diabetes or perinatal infections.

Mothers were recruited prenatally, and if the mother intended to feed the neonate formula, provided the neonate met the eligibility requirements at birth, the neonate was randomized after stratification by sex. For ethical and pragmatic reasons, neonates were not randomized to human milk or formula feeding. All formula-fed neonates received only the study formula immediately from birth through 2 weeks of age. Human milk-fed neonates did not receive supplemental formula at any time through 2 weeks of age. All neonate groups were concurrently studied to minimize any possible seasonal effects on calcium metabolism.^{2,3}

Each neonate had blood samples collected at 36 to 48 hours of age and on days 6 and 14 (± 1 day) of age. When possible, blood samples were drawn by venipuncture in the late morning 2 hours postprandially. Samples were collected in 5% carbon dioxide tubes to stabilize pH, and serum was separated for immediate ionized calcium measurement. The rest of the serum was frozen and analyzed in one batch for total calcium, phosphorus, and PTH concentrations. Serum ionized calcium concentrations were measured using an ion-selective electrode (Radiometer, Copenhagen, Denmark). The intra-assay and interassay coefficients of variation (CVs) on normal control serum are 0.8% and 2.5%, respectively. Serum total calcium concentrations were measured by atomic absorption spectrophotometry; the interassay CV is 2.1% to 2.5%. Serum phosphate concentrations were measured on an autoanalyzer (ABA-100, Abbott Diagnostics, Abbott Park, Ill). Our intra-assay and interassay CVs are 1.5% and 2.5%, respectively.

Intact PTH concentrations were measured using a modification of the method of Arnaud⁴ using guinea pig antiserum produced in our laboratory that recognizes the entire PTH molecule with no cross-reactivity with the 65-85 fragment or the 1-34 fragment. The intra-assay and interassay CVs are 8.4% and 16.3%, respectively.

Anthropometric measurements were obtained on days 2 and 14 of age. Dietary intakes were recorded daily for the first 14 days of life. The average daily phosphorus intake for days 1 to 6 and days 7 to 14 were calculated as the product of volume consumed and the phosphorus content of the formula divided by the number of days. The relationships between serum measurements at

6 and 14 days of age, and average phosphorus intakes during the week preceding the collection of blood samples, were determined. A specialized form of analysis of variance (ANOVA) techniques (nested) was performed that takes into account the repeated measurements obtained from a neonate.⁵ The factors included in the statistical model were diet, time, and the diet-by-time interaction. If this interaction is significant, it implies that the relationship, or changes over time, in the measurement differs depending on the diet of the neonate. In addition, Student's *t* test was performed to compare formula-fed and human milk-fed neonates at each time point. Analysis of variance was performed to determine whether there were differences between the three formula-fed groups at each time point. Biochemical measurements were normally distributed among human milk-fed neonates. However, serum PTH concentrations had a log normal distribution among formula-fed neonates. Statistical analyses using the log PTH concentration did not alter the findings. Data are presented as mean \pm SD.

RESULTS

The four groups were similar in weight and length at birth and 14 days of age, as well as in the percent of male neonates.

Formula-fed neonates had significantly lower serum ionized calcium concentrations than human milk-fed neonates (nested ANOVA, $P < .001$), and ionized calcium concentrations significantly increased over time (nested ANOVA, $P < .001$). The changes over time differed depending on the diet of the neonate (nested ANOVA interaction term, $P < .001$). Ionized calcium concentrations were lower in formula-fed neonates compared with human milk-fed neonates at both 6 and 14 days of age compared with human milk-fed neonates (Student's *t* test, $P < .001$ and $P = .001$, respectively; Fig 1). No differences were noted among the formula-fed groups (nested ANOVA, $P = .10$) in serum ionized calcium concentrations, and changes over time were similar among the groups (nested ANOVA interaction term, $P = .26$).

Serum total calcium level did not differ between formula- and human milk-fed neonates (nested ANOVA, $P = .10$) but did increase significantly with time (nested

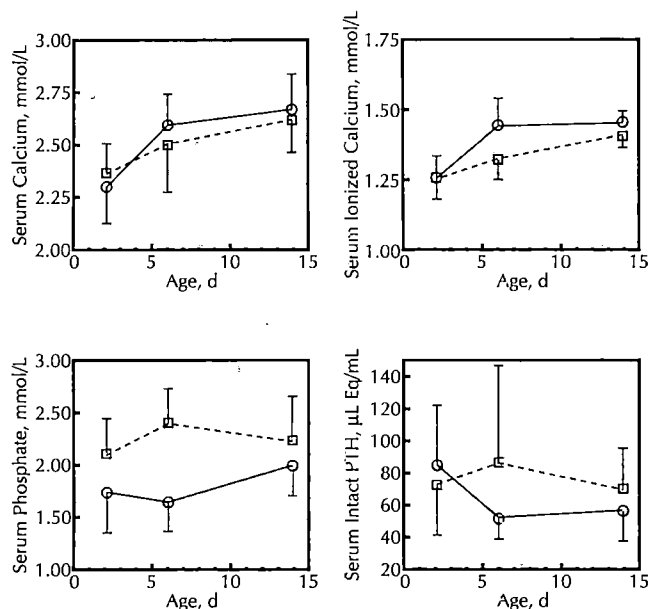


Fig 1.—Serum phosphate, calcium (total and ionized), and intact parathyroid hormone (PTH) concentrations in formula-fed neonates (squares) and human milk-fed neonates (circles). Data are presented as mean \pm SD. Overall, there was a significant effect of diet on serum ionized calcium ($P < .001$) and phosphate ($P < .001$) concentrations. Significant age effects were observed for serum ionized calcium ($P < .001$), total calcium ($P < .001$), and phosphate ($P < .001$) concentrations. The changes with age differed significantly by diet for serum ionized calcium ($P < .001$), total calcium ($P = .005$), phosphate ($P < .001$), and intact PTH ($P = .002$) concentrations.

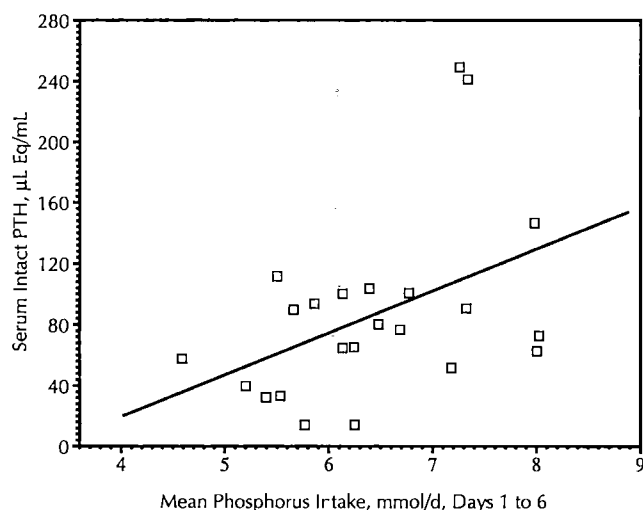


Fig 2.—Serum intact parathyroid hormone (PTH) level at 6 days of age was associated with average daily phosphorus intake from days 1 to 6 of age ($r = .436$, $P = .03$).

ANOVA, $P < .001$). This change over time differed between the formula- and human milk-fed groups (Fig 1; nested ANOVA interaction term, $P = .005$). There were no significant differences among the three formula-fed groups (nested ANOVA, $P = .92$) in serum total calcium concentrations (Table), and changes over time were similar among the groups (nested ANOVA interaction term, $P = .17$).

Neither serum ionized nor total calcium concentrations

on days 6 or 14 of age were related to the amount of phosphorus consumed (average in milligrams per day) during the first 6 or 14 days of age.

Formula-fed neonates had higher serum phosphate concentrations than human milk-fed neonates (nested ANOVA, $P < .001$), and serum phosphate concentrations changed significantly over time (nested ANOVA, $P < .001$). This change over time differed depending on the diet of the neonate (nested ANOVA interaction term, $P < .001$). Formula-fed neonates had higher serum phosphate levels on days 2 ($P < .001$) and 6 ($P < .001$) of age (Fig 1). No significant differences were noted among the three formula-fed groups (nested ANOVA, $P = .19$) in serum phosphate concentrations (Table), and changes over time were similar among the groups (nested ANOVA, $P = .88$). Serum phosphate concentrations on days 6 or 14 of age were not related to the phosphorus consumed during the first 6 or 14 days of age.

Overall, there was no difference in intact PTH concentrations between formula- and human milk-fed neonates (nested ANOVA, $P = .20$), and for all neonates combined there was no difference with time (nested ANOVA, $P = .13$). However, changes in serum PTH concentrations over time were different in formula-fed compared with human milk-fed neonates (nested ANOVA interaction term, $P = .002$): concentrations decreased between days 2 and 6 in neonates fed human milk, while they increased in neonates fed formula. There were no significant differences among the three formula-fed groups (nested ANOVA, $P = .87$) in serum intact PTH concentrations (Table), and changes over time were similar among the groups (nested ANOVA, $P = .34$). Serum C-terminal PTH concentrations were also measured. No significant results were found, and since C-terminal PTH represents inactive PTH fragments, the results are not presented.

Serum PTH concentration on day 6 of age was related to the phosphorus intake during the first 6 days of age ($r = .436$, $P = .03$; Fig 2). Serum PTH concentrations on day 14 of age were not related to the average phosphorus intake during the preceding 7 or 14 days ($r = .155$, $P = .47$ and $r = .121$, $P = .57$, respectively).

COMMENT

In a previous study, our laboratory reported the anecdotal occurrence of hypocalcemic convulsions, hyperphosphatemia, and elevated serum PTH concentrations in neonates fed modern humanized cow's milk-based formula.¹ Although secondary hyperparathyroidism is thought to occur in such neonates as a result of the lowering of serum calcium concentrations resulting from the high phosphate load, there have been no prospective studies evaluating sequential serum mineral and PTH concentrations in this situation.

Early reports from the United Kingdom linked the occurrence of "late" neonatal hypocalcemia and tetany to neonates receiving cow's milk-based formulas with high phosphorus content.^{6,7} Lealman and coworkers in Glasgow, Scotland,⁸ reported lower serum calcium and higher serum phosphate concentrations at 6 days of age in term neonates fed a humanized cow's milk-based formula (Cow and Gate V formula; phosphorus, 16 mmol/L; Ca/P molar ratio, 1.1) compared with neonates fed human milk (phosphorus, 4.8 mmol/L; Ca/P molar ratio, 1.6). Serum phosphate concentrations were not as high, and serum calcium concentrations not as low, as those respective measurements in neonates receiving an even higher phos-

phorus-containing cow's milk-based formula (Ostermilk; phosphorus, 20.6 mmol/L; Ca/P molar ratio, 1.0). Bagnoli and coworkers⁹ in Italy found that neonates fed cow's milk-based formula (phosphorus, 11.6 mmol/L; Ca/P molar ratio, 1.0) had lower total calcium and higher serum phosphate concentrations by 48 hours of age than human milk-fed neonates. In none of the above studies were serum PTH concentrations determined.

In the United States, late infantile tetany apparently has become less common since the introduction of humanized cow's milk-based proprietary formulas with lower phosphorus content. However, these humanized formulas still contain a higher phosphorus load and lower Ca/P molar ratio than that provided by human milk. It has been impossible to lower the phosphorus content further because of the phosphorus present in the protein, and owing to the low solubility of calcium, it has been difficult to incorporate higher amounts of calcium into formula to increase the Ca/P ratio. Thus, theoretically, since humanized cow's milk-based formulas still contain a phosphorus content relatively higher than that in human milk, the potential for high serum phosphate and low serum calcium concentrations in neonates fed these formulas still exists.

The phosphorus content in formula theoretically may affect calcium homeostasis either by forming insoluble calcium salts in the intestine, thereby reducing the availability of calcium, or by increasing serum phosphate concentrations once absorption has occurred.¹⁰ This increase in serum phosphate concentration would increase the calcium \times phosphate product in blood, promoting efflux of calcium and phosphate into bone, theoretically resulting in a lowering of blood ionized calcium concentrations. An increase in serum PTH concentrations theoretically will reduce (normalize) the high serum phosphate concentrations through its phosphaturic action and elevate (normalize) the low serum calcium concentrations through its bone and renal actions.

In this study, we observed a significant difference between formula- and human milk-fed neonates with respect to serum phosphate (higher in formula-fed neonates) and ionized calcium (lower in formula-fed neonates) concentrations. However, a dose-response relationship of increasing calcium concentrations or decreasing phosphorus concentrations with formulas of increasing Ca/P ratios was not observed. In addition, we observed a positive relationship between intact PTH concentrations on day 6 of age and the average amount of phosphorus consumed during the first 6 days of age. We suggest from our results that the amount of phosphorus consumed, rather than the Ca/P ratio of the formula, may be more important in altering calcium homeostasis in infancy. Larger amounts of phosphorus ingested thus indirectly trigger a PTH response, which normalizes serum calcium and phosphate concentrations.

Enhanced phosphate reabsorption by the immature kidney has been reported. It has been suggested that the mechanism for this enhanced renal phosphate reabsorption is the high concentration of growth hormone in the neonatal period¹¹ or possibly intracellular phosphate depletion in immature renal cells, thereby increasing apical membrane phosphate transport.¹² Thus, this maximal reabsorption of phosphate in the immediate neonatal period may in part explain the significant increase in serum phosphate concentrations related to a high phosphorus intake. This also might explain why late neonatal hypocalcemia

occurs primarily in the first week of age.

Although the differences between the means, especially for serum ionized calcium, do not appear large, the variation is small owing to the inherent biological need to maintain serum ionized calcium concentrations within a narrow range. These differences are significant from a public health viewpoint. A lower limit for ionized calcium of 1.10 mmol/L at 24 hours of age, a time when concentrations are the lowest, has been reported.¹³ Based on the means and SDs observed in the current study at 6 days of age, the proportion of the two populations that lie below this value may be estimated. The risk for hypocalcemia, defined as a serum ionized calcium concentration below 1.10 mmol/L, among neonates fed human milk is 1/10 000, compared with 30/10 000 among neonates fed formula. This difference may explain why hypocalcemic tetany is observed primarily in neonates fed formula and not human milk.

In this study, we have chosen the human milk-fed group as the reference, or "gold standard," with respect to infant feeding. The opposite opinion also could be presented: the volume of intake of formula-fed neonates could be considered the norm, and human milk-fed neonates could be receiving lower, inadequate intakes of phosphorus during the first week of age.

In summary, cow's milk-based formula feeding results in increased serum phosphate, decreased serum ionized calcium, and increased PTH levels compared with human milk feeding in the neonatal period. We speculate that late neonatal hypocalcemia, which can develop in some term neonates, may be related to use of cow's milk-based formula. Differences in calcium homeostasis between formula- and human milk-fed neonates in the neonatal period appear to be related to the high phosphorus content of formula relative to human milk rather than differences in Ca/P ratio.

This study was supported in part by grant 11725 from the National Institute of Child Health and Human Development, Bethesda, Md; the Cincinnati Perinatal Research Institute; and Ross Laboratories, Columbus, Ohio.

We would like to acknowledge the nurses in the Obstetric Unit of University of Cincinnati (Ohio) Medical Center for their assistance; the laboratory personnel for their technical expertise; and the mothers who participated for their support of medical research.

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BOOK REVIEW

An Introduction to Clinical Research

By Catherine DeAngelis, 183 pp, with illus, \$24.95, Stoneham, Mass, Butterworth Publishers Inc, 1991.

This is a clear, well-written book that walks the reader through a clinical research project. It begins with defining the research question and ends with critiquing the published project description. The author has consulted respected clinical researchers in writing this text, and her introduction is an excellent précis of the journey from the beginning to the end of a research project. Chapter 1, which discusses the scientific method, is the most difficult chapter to understand and could be simplified in the next edition.

Chapters 2 and 3 review the definition of the research question and selection of subjects. Chapter 4 ("Types of Research Models and Methods") is particularly good. It clarifies such difficult concepts as varied study designs by using excellent tables and figures. Chapter 5 discusses data collection, management, and analysis; like chapter 4, its clarification of topics such as statistical tests of significance and data collection methods is excellent. Chapter 6 discusses frequently asked questions about finding sources and about ethical standards for research involving human subjects, including federal regulations and criteria of institutional internal review boards.

A particular strength of this book is its success at remaining an *introduc-*

tion to clinical research. Each chapter contains references to books and articles that address particular issues more comprehensively. In addition, chapter 8 is an annotated bibliography providing a synopsis of books with particular relevance to research methods and development, statistics, clinical research funding, and critical appraisal of the medical literature.

This book should be a valued addition to the library of junior faculty, physicians on fellowship, residents, and any student in the health profession who is interested in understanding and performing clinical research.

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Evaluation of Intraosseous vs Intravenous Antibiotic Levels in a Porcine Model

David G. Jaimovich, MD; Ashir Kumar, MD; Steve Francom, PhD

• **Objectives.**—To compare intraosseous vs intravenous routes of administration and their effects on serum levels of four antibiotics in an animal model.

Design.—Prospective controlled study comparing two routes of drug administration.

Setting.—Research laboratories of a large pharmaceutical company.

Participants.—Twenty male and female domestic swine weighing 10 to 20 kg.

Interventions.—The animals were anesthetized and treated with controlled ventilation. The animals were divided into one of four groups: (1) intravenous and intraosseous cefotaxime sodium (50 mg/kg), (2) intravenous and intraosseous chloramphenicol sodium succinate (25 mg/kg), (3) intravenous and intraosseous vancomycin hydrochloride (15 mg/kg), or (4) intravenous and intraosseous tobramycin sulfate (2.5 mg/kg). There was a 24-hour clearance period for groups 1 and 2 and a 48-hour clearance period for groups 3 and 4. Serum drug levels were measured at 1, 15, 30, 45, 60, 90, and 120 minutes

after intravenous and intraosseous administration of the respective antibiotics. Control and treated tibias were sampled for drug levels at the end of the experiment.

Measurements and Main Results.—Peak serum concentrations for intravenously administered antibiotics were within the therapeutic range. Peak serum levels after intravenous and intraosseous administration were 102 and 82 mg/L, respectively for cefotaxime; 13.9 and 6.3 mg/L, respectively, for chloramphenicol; 24.5 and 3.8 mg/L, respectively, for vancomycin; and 7.1 and 1.3 mg/L, respectively, for tobramycin.

Conclusions.—Cefotaxime may be administered intraosseously when intravenous access is not possible. We cannot recommend chloramphenicol or vancomycin for intraosseous administration, because serum levels were not comparable with those following intravenous administration. Findings with tobramycin suggested a lack of achievement of serum levels comparable with those following intravenous administration.

(AJDC. 1991;145:946-949)

Infants and children with fulminant bacterial infection often present in septic shock.¹ If intravenous (IV) access is not readily available for administration of volume expanders and antimicrobial agents, morbidity and mortality are adversely affected.² In recent years, there has been a resurgence of the intraosseous (IO) route for the administration of a variety of drugs that may need to be administered urgently.³⁻⁵ The IO route was first utilized for administration of fluids and blood almost half a century ago but was virtually abandoned because of the availability of "fine butterfly" needles and IV catheters.^{6,7} Some drugs, when administered IO, achieve therapeutic serum levels; others, however, fail to do so.⁸ Recently, Jaimovich et al⁸ reported that serum levels of phenobarbital sodium and phenytoin sodium, when administered IO, were markedly lower than when these anticonvulsant drugs were administered IV. Furthermore, phenytoin, when ad-

ministered IO, failed to achieve therapeutic serum levels and therefore could not be recommended for IO administration. Despite a large number of antimicrobial drugs available today, no data regarding serum levels achieved after the IO administration of an antibiotic are readily available. We compared IO vs IV routes and their effects on serum levels of four antibiotics in an animal model.

MATERIALS AND METHODS

The animals were housed in the animal care facility of the Upjohn Research Facility, Kalamazoo, Mich, in accordance with their institutional animal care guidelines. Twenty domestic swine weighing 10 to 20 kg were anesthetized with ketamine hydrochloride (20 mg/kg given intramuscularly). The animals were then given inhalation anesthesia with halothane. Subsequently, the trachea was intubated with a No. 5 or 6 endotracheal tube, ventilation was controlled, and halothane anesthesia was continued. Lead II electrocardiography monitored heart rate and rhythm throughout the experiment. Two peripheral hind limb veins were cannulated with 20-gauge catheters for administration of IV fluids as necessary and for administration of the antibiotics, respectively. The jugular vein was catheterized to obtain serum samples for antibiotic levels. Intravenous fluids were administered as 5% dextrose in water at a rate of 4 mL/kg per hour; temperature was maintained between 37°C and 38°C. The animals were randomly assigned to one of the four study groups: (1) IV and IO cefotaxime sodium, (2) IV and IO chloramphenicol sodium succinate, (3) IV and IO vancomycin hydrochloride, and (4) IV and IO tobramycin sulfate.

Accepted for publication February 4, 1991.

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Reprint requests to the Department of Pediatrics (M/C 856), Division of Critical Care, University of Illinois, 840 S Wood St, Chicago, IL 60612 (Dr Jaimovich).

After skin preparation, a 16-gauge adjustable-length bone marrow aspiration needle (Monoject Illinois Sternal-Iliac, Sherwood Medical, St Louis, Mo) was inserted into the broad, flat, anteromedial surface of the tibia 1 cm below the tibial tuberosity. Once the needle was advanced into the bone marrow, the obturator was removed, and the IO position of the needle was confirmed by free aspiration of blood and bone marrow contents, such as fat and bone spicules. All animals received a 10-mL saline solution flush to clear the cannula of the antibiotic after IO administration.

The first study group ($n=5$) was given cefotaxime sodium (50 mg/kg) through a peripheral IV line, and a similar dose was administered via the IO route. The second group ($n=5$) was given chloramphenicol sodium succinate (25 mg/kg) IV and IO. There was a 24-hour serum clearance period between the IV and IO administrations of cefotaxime and chloramphenicol. The third group ($n=5$) was administered vancomycin hydrochloride (15 mg/kg) IV and IO. The fourth group ($n=5$) received tobramycin sulfate (2.5 mg/kg) IV and IO. There was a 48-hour serum clearance period between the IV and IO administrations of vancomycin and tobramycin. The animals were allowed to recover in their pens and were reanesthetized in similar fashion for the IO phase of the study. Cefotaxime, chloramphenicol, and tobramycin were administered during a 30-minute period, and vancomycin was administered during a 60-minute period. Blood, to measure serum antibiotic levels for each drug, was drawn from the jugular venous line at 1, 15, 30, 45, 60, 90, and 120 minutes after the administration of the respective antibiotics by both the IV and the IO routes. An additional pretreatment serum level, before IO administration, was measured to verify drug clearance from the serum. All animals were killed at the end of the experiment per Upjohn Research facility protocol.

Cefotaxime serum levels were assayed by high-pressure liquid chromatography by solvent delivery system (Water's 501 Pump), with a sample injector (Water's U6K Injector), cefotaxime levels were detected by a UV spectrophotometer (Water's 481 Spectrophotometer Water's Associates, Milford, Mass), and recorded on a strip chart recorder (Omniscrite Inc, Houston, Tex). Serum samples and standards were processed by phase extraction and injected into the system with a mobile phase of 8% acetonitrile and 92% 0.1-mol/L potassium phosphate buffer. Peak heights were measured and specimen valleys were calculated according to the standard curve. Validation of the procedure yielded within-batch and between-batch reproducibility of greater than 95%. Serum for chloramphenicol was analyzed by submitting samples into a delivery system (SYVA Auto Carousel, SYVA Company, Palo Alto, Calif). Chloramphenicol levels were detected by a UV spectrophotometer (S-III Spectrometer, SYVA Company), and drug level calculations were computer analyzed (Lab Processor 6500, SYVA Company). Samples were analyzed along with standards and quality control materials with emit reagents (SYVA Emit Assay, SYVA, Company). This assay is a homogeneous enzyme immunoassay technique based on competition between drug in the sample and enzyme-labeled drug. This assay has a within-run coefficient of variance of 4% and a between-run coefficient of variance of 5%. Tobramycin and vancomycin were tested by fluorescent polarization (TDX Analyzer, Abbott Diagnostics, North Park, Ill). Samples were analyzed along with quality control materials with the use of reagent packs (Abbott Diagnostics) according to the manufacturer's specifications. The analyzer utilizes fluorescent polarization immunoassay technology. Both assays have between- and within-run coefficients of variance of less than 5%.

Control contralateral tibias and the tibias into which antibiotics were administered were frozen in liquid nitrogen, crushed, and then homogenized. The tibia into which chloramphenicol was administered was placed in a 100-mL solution of methanol and extracted with a high-speed tissue homogenizer. The extract was centrifuged at 2000g for 10 minutes. The resulting supernatant was then submitted for enzyme immunoassay, and the concentration was determined by UV spectrophotometry and computer analysis. Samples from the tibias that received intraosseous to-

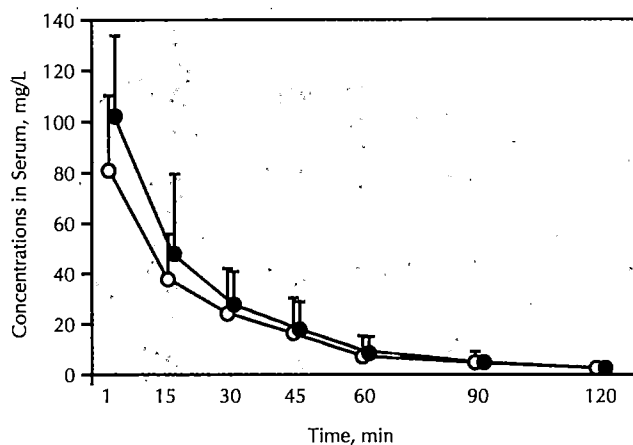


Fig 1.—Serum concentrations of cefotaxime over time following intravenous (solid circles) and intraosseous (open circles) routes of administration.

Pharmacokinetic Data Following Intravenous and Intraosseous Routes of Administration*			
Drug	Intravenous	Intraosseous	P
Cefotaxime			
AUC	2673 ± 923	2347 ± 931	NS
C _{max}	102 ± 32	82 ± 27	NS
T _{max}	1.0 ± 0.0	1.0 ± 0.0	NS
Tobramycin (n=4)			
AUC	268 ± 182	62 ± 38	NS
C _{max}	7.1 ± 5.4	1.3 ± 0.7	NS
T _{max}	1.0 ± 0.0	12 ± 22	NS
Chloramphenicol			
AUC	753 ± 182	299 ± 138	.006
C _{max}	14.0 ± 1.8	6.4 ± 3.3	.005
T _{max}	1.0 ± 0.0	1.0 ± 0.0	NS
Vancomycin			
AUC	1598 ± 876	234 ± 281	.025 (n=4)
C _{max}	25 ± 13	3.8 ± 3.2	.023
T _{max}	1.0 ± 0.0	28 ± 52	NS

*Values are mean ± SD. AUC indicates area under the plasma concentration time curve; C_{max}, T_{max}; and NS, not significant.

bramycin and vancomycin infusions were prepared with a similar procedure, with the exception of the solvent. The frozen, crushed tibias were homogenized with 200 mL of a 0.01-mol/L sodium phosphate (pH 8.0) and placed in a refrigerated continuous rotor device that stirred the solution for 24 hours. The resulting supernatants were submitted and the concentrations were determined by fluorescent polarization immunoassay.

Statistical analysis was used to compare the means of the serum levels at each time point between the two routes of administration for each antibiotic. This was performed by using an analysis of variance model that incorporated factors for animals and route of administration. The pharmacokinetic data associated with antibiotic serum levels, maximum concentration (C_{max}), and the time to peak plasma concentration (T_{max}) were determined by inspection. The area under the plasma concentration time curve (AUC) was estimated with the trapezoid rule.

RESULTS

All animals survived the experiment with no adverse effects noted clinically from the IV and IO administration of antibiotics. At no time during the experiment did any

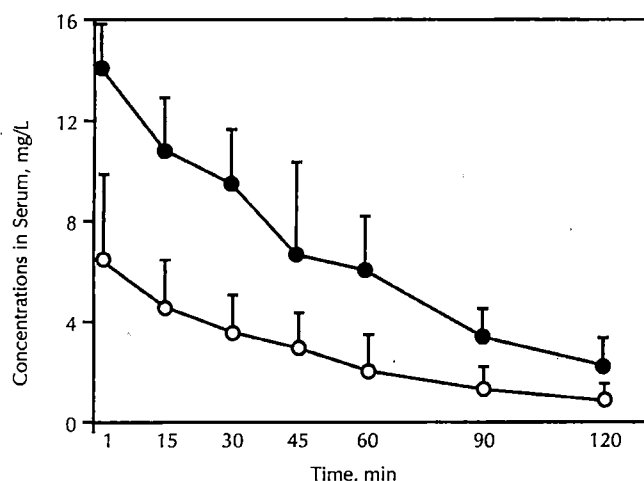


Fig 2.—Serum concentrations of chloramphenicol over time following intravenous (solid circles) and intraosseous (open circles) routes of administration.

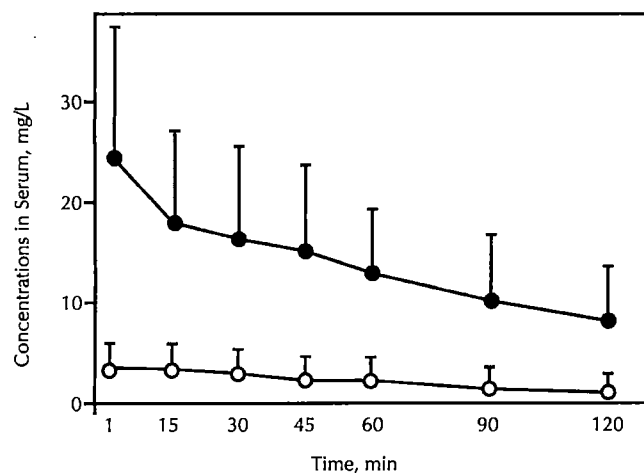


Fig 3.—Serum concentrations of vancomycin over time following intravenous (solid circles) and intraosseous (open circles) routes of administration.

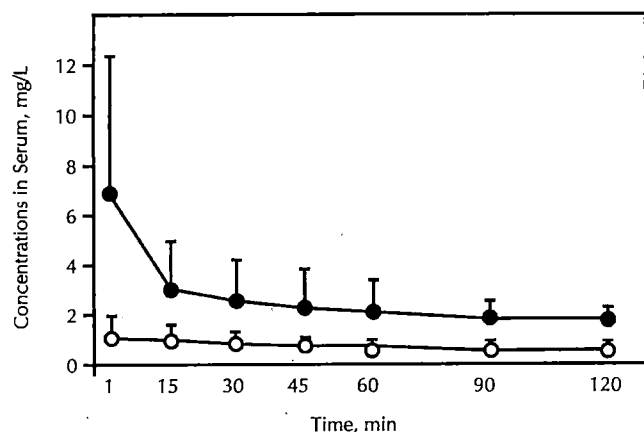


Fig 4.—Serum concentrations of tobramycin over time following intravenous (solid circles) and intraosseous (open circles) routes of administration.

of the animals exhibit signs of deterioration in cardiovascular, hemodynamic, or pulmonary status.

The means, SDs, and *P* values associated with the various drugs, routes of administration, and pharmacokinetic data are seen in the Table. Serum cefotaxime levels following the IV and IO routes of administration showed the

curve to be nearly identical, and there were no significant differences (Fig 1, Table, $P < .01$) and vancomycin ($P < .05$) showed significant differences between the IV and the IO routes of administration for C_{max} and AUC (Table, Figs 2 and 3). Although the differences for C_{max} and AUC were not statistically significant ($P > .15$) between the two routes, for tobramycin, the peak achieved after the IO route of administration was only 1.3 mg/L (Fig 4). Tobramycin had a lower power due to one less subject in the study group.

The level of chloramphenicol in the tibia receiving the IO administration after 120 minutes of infusion was 253.8 mg/L, and the contralateral (control) tibia showed a level of 42.4 mg/L. The vancomycin level in the tibia at 120 minutes after the IO infusion was 28.6 mg/L, and the control tibia showed a level of 3.08 mg/L. Similarly, the tobramycin level in the tibia at 120 minutes after the IO infusion was 0.81 mg/L, and the control tibia showed a level of 0.20 mg/L. Bones for cefotaxime levels were not assayed due to the near-identical serum levels achieved following the IO and IV routes of administration of cefotaxime.

COMMENT

The peak serum concentration achieved following the administration of recommended IV dosages was within the therapeutic range and was also similar to the levels achieved in infants and children after the administration of a single dose for all four antibiotics.⁹ Serum levels achieved after IO administration were subtherapeutic for vancomycin, chloramphenicol, and tobramycin; however, the serum concentration of cefotaxime was comparable with the levels measured following IV administration. This subtherapeutic phenomenon has also been demonstrated when phenytoin was administered IO.⁸ Several-fold higher concentrations of chloramphenicol (sixfold), tobramycin (fourfold), and vancomycin (ninefold) were detected, even after 120 minutes in the respective tibias where these antibiotics were administered IO. These observations indicate that these three antibiotics were not fully distributed into the systemic circulation from the site of the administration. Chemical characteristics of antibiotics (ie, fat solubility, protein binding, and calcium binding) may influence the distribution of antibiotic from the IO space to the systemic circulation. These factors remain poorly understood. In critically ill children, the IO administration provides an alternate route to obtain vascular access when IV access is not readily available. The IO route is used to administer a variety of drugs; however, very limited data are available regarding serum concentrations of drugs achieved after IO administration.^{4,8,10} Domestic swine were chosen as the experimental model because of similarities between their tibias and those of infants. The weight and development of the bone marrow of 10- to 14-week-old swine are similar to those of infants or small children.³ In our study, only one of the four antibiotics evaluated achieved a comparable serum concentration when administered IO; therefore, we recommend that pharmacokinetic data be obtained for the drugs that may need to be administered through the IO route in an emergency. Our study demonstrated that cefotaxime, a third-generation cephalosporin with a broad spectrum of activity and that is capable of good central nervous system penetration in the presence of meningeal inflammation, achieved comparable levels in serum after IO administration. A large number of third-generation cephalosporins

and other antimicrobial drugs are available to pediatricians to treat critically ill infants and children. The physician should be aware that cefotaxime achieved comparable levels in the serum after IO and IV routes of administration.

This investigation was funded by the Bronson Clinical Investigation Unit Community Research Fund.

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PENNSYLVANIA – Pediatrician needed. \$130,000 net plus M/P insurance, full benefits, new office and operating expenses provided. One in four call. Built-in referrals. Population 200,000. Must be a dynamic self-starter interested in clinical practice development, recruiting pediatricians, development of pediatric services clinic. Must be board-certified. Call or send CV to: Perry Robinson, Cejka & Co., 222 South Central, Suite 700, St. Louis, MO 63105. (800) 765-3055.

HAWAII – PEDIATRICIAN: Opportunity with an established and growing multi-specialty group practice. Competitive compensation and excellent benefits. If working with congenial associates in a quality oriented environment is for you, why not consider relocating to the Hawaiian Islands? Send CV or call: Rex Couch, MD, Medical Director, Kauai Medical Group, Inc., 3420-B Kuhio Highway, Lihue, HI 96766. (808) 246-1624.

AUSTIN, TEXAS – Seeking general pediatrician BE/BC for full time position. Call or write: Mrudula Deshpande, MD, 13740 Research, V-1, Austin, TX 78750. (512) 250-0406.

Professional Opportunities

PEDIATRICIAN: Five person group seeking full-time BE/BC pediatrician. Fully equipped office in Lexington, Kentucky. Nearby tertiary care residency program. Competitive salary and benefit package. Send CV: M.J. Harris, Pediatric & Adolescent Associates, 2620 Wilhite Drive, Lexington, KY 40503.

PEDIATRIC NEUROLOGIST to direct sub-specialty program – The Section of Child Neurology at the Cleveland Clinic Foundation is seeking a BE/BC child neurologist to develop and direct a program either in neuromuscular disorders or genetic/metabolic disorders. Fellowship training or experience in the subspecialty of either neuromuscular disorders or genetic/metabolic disorders is highly desirable. This is an outstanding opportunity to join a premier clinical neurology and child neurology group with a strong commitment to education and research. Interested individuals should send a CV and three references to: A. David Rothner, MD, Head, Section of Pediatric Neurology, The Cleveland Clinic Foundation, Desk S71, One Clinic Center, Cleveland, OH 44195-5223. The Cleveland Clinic Foundation is an equal opportunity/affirmative action employer.

PHYSICIAN WANTED: Must have completed an approved American Residency Training program. Prefer physicians who are board-certified/board-eligible in family practice, internal medicine or pediatrics. Competitive salary complemented by state benefits. Contact: Medical Director, Winfield State Hospital and Training Center, R.R. #1, Box 123, Winfield, KS 67156. (316) 221-1200, Extension 311. EOE.

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Professional Opportunities

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Directors Wanted

NEONATOLOGIST: Director for a 6.5 member community section within the Division of Neonatology of the State University of New York at Buffalo. Using nurse practitioners, the section will provide coverage for a 12-bed Level II Nursery and two Level I Nurseries with a total of 8,500 deliveries. Its members will also rotate through the Level III Nursery and teach fellows, residents and nurse practitioners. The Division of Neonatology currently has ten faculty members and covers a 75-bed Level III Nursery. It conducts NIH sponsored laboratory research and clinical research including six years of experience with surfactant therapy. Contact: Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. (716) 878-7673. Affirmative action/equal opportunity employers.

PHILADELPHIA – Children's Seashore House, a regional pediatric rehabilitation hospital adjacent to and affiliated with The Children's Hospital of Philadelphia, is recruiting a pediatrician trained in developmental pediatrics, chronic diseases or general academic pediatrics, to serve as director of inpatient services. Opportunities are available for pursuit of teaching and clinical research interests. Candidate may be eligible for academic appointment (assistant or associate professor) in the Department of Pediatrics at the University of Pennsylvania School of Medicine. The University of Pennsylvania and the Children's Seashore House are equal opportunity, affirmative action employers. Interested candidates should submit a CV and three letters of reference to: Mark L. Batshaw, MD, Children's Seashore House, 3405 Civic Center Boulevard, Philadelphia, PA 19104. Position is available as of July 1, 1991.

Faculty Positions

WYOMING – University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, board-certified pediatrician to be the pediatric coordinator of an 8-8 family practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming! Contact: Dr. David Driggers, Director, University of Wyoming Family Practice Residency, 1522 East "A" Street, Casper, WY 82601. (307) 266-3076. The University of Wyoming is an affirmative action/EOE.

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THE DEPARTMENT OF PEDIATRICS of the University of Pittsburgh and Children's Hospital of Pittsburgh seeks a BC/BE pediatrician at the assistant or associate professor level to join the University Pediatric Diagnostic Referral Service. The position requires an academic generalist preferably with either chief residency experience or general academic pediatric fellowship training. Responsibilities include patient care, teaching, and clinical research, with an emphasis on inpatient care. Rank and salary commensurate with experience. Inquiries should be addressed to: J. Carlton Gartner, Jr., MD, University Pediatric Diagnostic Referral Service, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-3417. An equal opportunity employer.

DEPARTMENT OF PEDIATRICS, State University New York at Buffalo/Children's Hospital seeks faculty member to join ten member Division of Neonatology. We are seeking a physician with a commitment to pursue research which can be related to perinatal circulatory physiology. We are particularly interested in the responsibility of and remodeling of the pulmonary vascular bed of the fetus and newborn. Techniques employed could range from integrated physiologic, to isolated organ or tissue, to cellular or molecular. Division conducts NIH-sponsored laboratory research on perinatal pulmonary and circulatory physiology. Clinical research includes six years of experience with surfactant therapy. MD: BE/BC neonatal-perinatal medicine. Assistant or associate professor level. CV to Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. We are interested in identifying qualified minority and women candidates. The State University of New York at Buffalo and the Children's Hospital of Buffalo are affirmative action/equal opportunity employers. No person, in whatever relationship with the University or the Hospital, shall be subject to discrimination on the basis of age, creed, color, handicap, national origin, race, religion, sex, marital, or veteran status.

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Medical Center at Knoxville

Thomas D. Miale, M.D.
Associate Professor and Director
Hematology-Oncology Section
Department of Pediatrics, D-113
The University of Tennessee Medical Center
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Knoxville, TN 37920

or call collect (615) 544-9847 for further information.

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Faculty Positions

PEDIATRICIAN—TENNESSEE. Vanderbilt University Medical Center Pediatrics Department seeks developmental/behavioral pediatrician for Division of Child Development at assistant or associate professor level. Responsibilities: Interdisciplinary team evaluations, clinical teaching, opportunity to pursue research. Reply to: Mark Wolraich, MD, Chief, Division of Child Development, 426 Medical Center South, 2100 Pierce Avenue, Nashville, TN 37232-3573.

PEDIATRICIAN—Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence E. Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

Faculty Positions

JUNIOR FACULTY POSITION in the Division of General/Ambulatory Pediatrics is available at Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas. Applicant must be board-eligible/-certified. Responsibilities include teaching, patient care and clinical research. Tenure track appointment available to qualified candidates. Call or submit CV to: V.J. Gururaj, MD, Professor, Director Division General/Ambulatory Pediatrics, Texas Tech University Health Sciences Center, School of Medicine, Department of Pediatrics, Lubbock, TX 79430. (806) 743-2266.

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The AMERICAN JOURNAL OF DISEASES OF CHILDREN (ISSN 0002-922X) is published monthly by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing office.

CHANGE OF ADDRESS—POSTMASTER, send all address changes to AMERICAN JOURNAL OF DISEASES OF CHILDREN, Attention: Subscription Department, 515 N State St, Chicago, IL 60610. Notification of address change must be made at least 6 weeks in advance. Include both old and new addresses, a recent mailing label, and your new ZIP code.

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CLINICAL PHARMACOLOGY: IPOL is a highly purified, inactivated poliovirus vaccine produced by microcarrier culture.^{1,2} This culture technique and improvements in purification, concentration and standardization of poliovirus antigen have resulted in a more potent and more consistently immunogenic vaccine than the Poliovirus Vaccine Inactivated which was available in the U.S. prior to 1988. These new methods allow for the production of vaccine that induces antibody responses in most children after administering fewer doses³ than with vaccine available prior to 1988.

Studies in developed⁴ and developing⁵ countries with a similar inactivated poliovirus vaccine produced by the same technology have shown that a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer.

A study in the U.S. was carried out, which involved 219 two-month-old infants who had received three doses of Poliovirus Vaccine Inactivated manufactured by the same process as IPOL except the cell substrate was primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine. Following a third dose of vaccine at 18 months of age, high titers of neutralizing antibody were present in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.⁶

Additional studies were carried out in the U.S. with IPOL. Results were reported for 120 infants who received two doses of IPOL at 2 and 4 months of age. Of these 120 children, detectable serum neutralizing antibody was induced after two doses of vaccine in 98.3% (Type 1), 100% (Type 2) and 97.5% (Type 3) of the children. In 83 children receiving three doses at 2, 4, and 12 months of age detectable serum neutralizing antibodies were detected in 97.6% (Type 1) and 100% (Types 2 and 3) of the children.^{7,8}

Poliovirus Vaccine Inactivated reduces pharyngeal excretion of poliovirus.⁹⁻¹² Field studies in Europe have demonstrated immunity in populations thoroughly immunized with another IPV.¹³⁻¹⁷ A survey of Swedish children and young adults given a Swedish IPV demonstrated persistence of circulating antibodies for at least 10 years to all three types of poliovirus.¹³

Paralytic polio has not been reported in association with administration of Poliovirus Vaccine Inactivated.

INDICATIONS AND USAGE: Poliovirus Vaccine Inactivated is indicated for active immunization of infants, children and adults for the prevention of poliomyelitis. Recommendations on the use of live and inactivated poliovirus vaccines are described in the ACIP Recommendations^{18,19} and the 1988 American Academy of Pediatrics Red Book.²⁰

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations: It is recommended that all infants, unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.¹⁸ Poliovirus Vaccine Inactivated should be offered to individuals who have refused Poliovirus Vaccine Live Oral Trivalent (OPV) or in whom OPV is contraindicated. Parents should be adequately informed of the risks and benefits of both inactivated and oral polio vaccines so that they can make an informed choice (Report of an Evaluation of Poliomyelitis Vaccine Policy Options, Institute of Medicine, National Academy of Sciences, Washington, D.C., 1988).

OPV should not be used in households with immunodeficient individuals because OPV is excreted in the stool by healthy vaccinees and can infect an immunocompromised household member, which may result in paralytic disease. In a household with an immunocompromised member, only Poliovirus Vaccine Inactivated should be used for all those requiring poliovirus immunization.²⁰

Children Incompletely Immunized: Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see DOSAGE AND ADMINISTRATION).

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with Poliovirus Vaccine Inactivated.

ADULTS

General Recommendations: Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the U.S. is not recommended. Adults who have increased risk of exposure to either vaccine or wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the DOSAGE AND ADMINISTRATION section.¹⁸

The following categories of adults run an increased risk of exposure to wild polioviruses:¹⁹

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.
- Incompletely vaccinated or unvaccinated adults in a household (or other close contacts) with children given OPV provided that the immunization of the child can be assured and not unduly delayed. The adult should be informed of the small OPV related risk to the contact.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

Patients with recognized immunodeficiency are at greater risk of developing paralysis when exposed to live poliovirus than persons with a normal immune system. Under no circumstances should oral live poliovirus vaccine be used in such patients or introduced into a household where such a patient resides.¹⁸

Poliovirus Vaccine Inactivated should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antineoplastic or radiation. Patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of Poliovirus Vaccine Inactivated.²¹

CONTRAINDICATIONS: Poliovirus Vaccine Inactivated is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including neomycin, streptomycin and polymyxin B.

If anaphylaxis or anaphylactic shock occurs within 24 hours of administration of a dose of vaccine, no further doses should be given.

Vaccination of persons with any acute, febrile illness should be deferred until after recovery; however, minor illnesses such as mild upper respiratory infections are not in themselves reasons for postponing vaccine administration.

WARNINGS: Neomycin, streptomycin, and polymyxin B are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see DESCRIPTION) and allergic reactions may occur in persons sensitive to these substances.

PRECAUTIONS: General: Before injection of the vaccine, the physician should carefully review the recommendations for product use and the patient's medical history including possible hypersensitivities and side effects that may have occurred following previous doses of the vaccine.

Epinephrine hydrochloride (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Concerns have been raised that stimulation of the immune system of a patient with HIV infection by immunization with inactivated vaccines might cause deterioration in immunologic function. However, such effects have not been noted thus far among children with AIDS or among immunosuppressed individuals after immunizations with inactivated vaccines. The potential benefits of immunization of these children outweigh the undocumented risk of such adverse events.¹⁸

Drug Interactions: There are no known interactions of Poliovirus Vaccine Inactivated with drugs or foods. Simultaneous administration of other parenteral vaccines is not contraindicated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY: REPRODUCTIVE STUDIES — PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with Poliovirus Vaccine Inactivated. It is also not known whether Poliovirus Vaccine Inactivated can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Poliovirus Vaccine Inactivated should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE: Safety and efficacy of IPOL have been shown in children 6 weeks of age and older^{8,9} (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed during a clinical trial.⁶ Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures $\geq 39^{\circ}\text{C}$ ($\geq 102^{\circ}\text{F}$) were reported in up to 38% of vaccinees. Other symptoms noted included sleepiness, fussiness, crying, decreased appetite, and spitting up of feedings. Because Poliovirus Vaccine Inactivated was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given without IPV.

In another study using IPOL in the United States, there were no significant local or systemic reactions following injection of the vaccine. There were 7% (6/86), 12% (8/65) and 4% (2/45) of children with temperatures over 100.6°F, following the first, second and third doses respectively. Most of the children received DTP at the same time as IPV and therefore it was not possible to attribute reactions to a particular vaccine; however, such reactions were not significantly different than when DTP is given alone.

Although no causal relationship between Poliovirus Vaccine Inactivated and Guillain-Barré Syndrome (GBS) has been established,²² GBS has been temporally related to administration of another Poliovirus Vaccine Inactivated.

NOTE: The National Childhood Vaccine Injury Act of 1986 requires the keeping of certain records and the reporting of certain events occurring after the administration of vaccine, including the occurrence of any contraindicating reaction. Poliovirus Vaccines are listed vaccines covered by this Act and health care providers should ensure that they comply with the terms thereof.²³

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration. If these conditions exist, vaccine should not be administered.

After preparation of the injection site, immediately administer the vaccine subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In adults the vaccine should be administered in the deltoid area.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

CHILDREN

Primary Immunization: A primary series of IPOL consists of three 0.5 ml doses administered subcutaneously. The interval between the first two doses should be at least four weeks, but preferably eight weeks. The first two doses are usually administered with DTP immunization and are given at two and four months of age. The third dose should follow at least six months but preferably 12 months after the second dose. It may be desirable to administer this dose with MMR and other vaccines, but at a different site, in children 15-18 months of age. All children who received a primary series of Poliovirus Vaccine Inactivated, or a combination of IPV and OPV, should be given a booster dose of OPV or IPV before entering school, unless the final (third dose) of the primary series was administered on or after the fourth birthday.¹⁸

The need to routinely administer additional doses is unknown at this time.¹⁸

A final total of four doses is necessary to complete a series of primary and booster doses. Children and adolescents with a previously incomplete series of IPV should receive sufficient additional doses to reach this number.

ADULTS

Unvaccinated Adults: For unvaccinated adults at increased risk of exposure to poliovirus, a primary series of Poliovirus Vaccine Inactivated is recommended. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, 3 doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. If less than 1 month is available, a single dose of either OPV or IPV is recommended.

Incompletely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than 3 doses of conventional IPV or a combination of conventional IPV or OPV totaling fewer than 3 doses should receive at least 1 dose of OPV or Poliovirus Vaccine Inactivated. Additional doses needed to complete a primary series should be given if time permits.

Completely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of either OPV or IPV.¹⁹

HOW SUPPLIED: Syringe, 0.5 ml with integrated needle (1 x 1 Dose package and 10 x 1 Dose package)—Product Nos. 49281-8605-1 and 49281-8605-2.

STORAGE: The vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F and 46°F). The vaccine must not be frozen.

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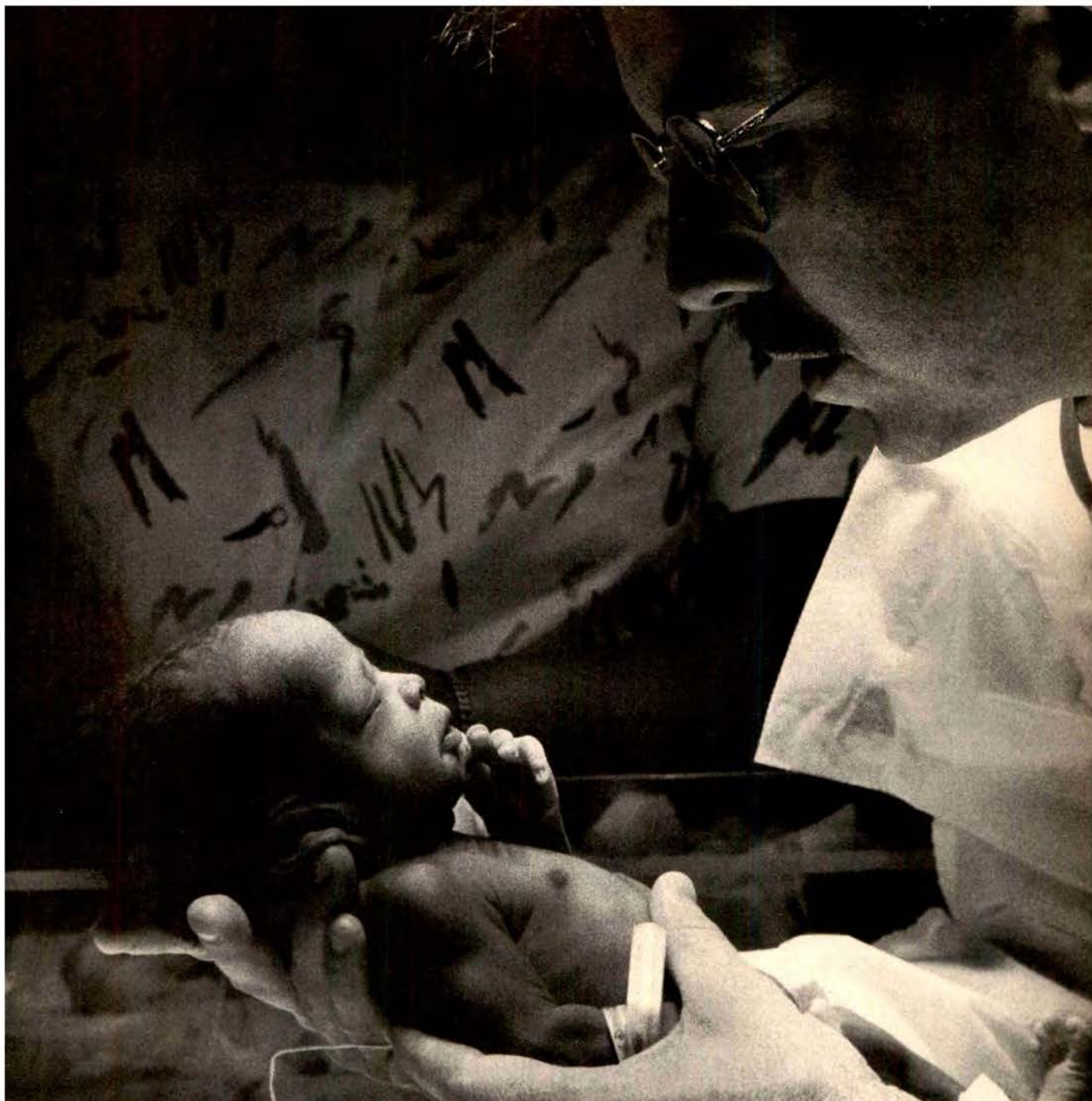
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Family Physicians and Neonatology

Sir.—It is regrettable that the editor who edits this section of *THE JOURNAL* is so ignorant of interspecialty relations that he or she would not have purged the slur to family practitioners in the letter by DiTraglia¹ that appeared in the November 1990 issue.

All specialties contribute in unique ways to the care of the patient. I am convinced that there are medical and family issues that family practitioners handle better than pediatricians, because of the family physician's involvement with other family members and in other acute care settings. One example is of a 4-year-old girl who presented with chest pains and was recognized by her family physician to have an acute myocardial infarction, despite the pediatricians' diagnoses. I guess I have participated in the resuscitation of more newborns in the last 10 years than many pediatric oncologists, yet I would not disparage another specialty because of disparate practice patterns.

The general pediatricians and pediatric subspecialists who trained me were intent on spreading good pediatric care to the most children who could be reached. This should remain our common goal rather than slandering each other, especially in eminent journals.

FLOYD L. MCINTYRE, MD
Family Medicine
76 Airline Rd
South Dennis, MA 02660

1. DiTraglia J. Neonatology blues. *AJDC*. 1990;144:1180.

In Reply.—I am sorry that McIntyre considers my statement a slur. It was not intended to be derogatory.

He states that we all offer unique care to children; this is what I meant. Even within specialties, different in-

dividuals have different strengths and training backgrounds.

I am comfortable with my role as a pediatrician and with the unique contribution I make to the care of patients. I hope McIntyre is not insecure with his role as a family practitioner in his community.

JOHN DiTRAGLIA, MD
1835 Oakland Ave Bldg A
Portsmouth, OH 45662

Your Child's Best Friend: TV or Not TV?

Sir.—In the March 1991 issue of *AJDC*,¹ Dr Stiehm described his experience with strict curtailment of his three daughters' TV viewing so that they would devote more time to schoolwork, reading, music, and exercise. This worked out well for his family, but it might not for others who have different interests and/or lack entertainment and learning alternatives.

Television has been stigmatized as the "boob tube," yet it also provides fine educational, news, public affairs, sports, music, and general entertainment programs. One must be selective to find good books in a library and good music on the radio; this also applies to TV programs. Thus, rather than proscribe TV, parents might be better advised to review the coming weeks' TV fare, go over it with their children, and help them decide which programs of value to watch. Clearly, there is nothing wrong with children viewing "Sesame Street"; "Mister Rogers"; "NoVA"; "The National Geographic Explorer"; telecourses; plays, such as *The Grapes of Wrath* and *Hamlet*; selected well-regarded movies and docudramas; operas, concerts, "Live From Lincoln Center"; "Evening at Pops"; "20/20"; "60 Minutes"; "The Civil War" series; "The Cosby Show"; a sports event or two; and the news, including Cable News

Network's coverage of events such as the Persian Gulf war.

Television is a major educational tool for many people and may be their only real contact with the outside world. (About 30% of US families do not subscribe to a newspaper.) It is the only entertainment many families can afford. A large number of TV viewers are latchkey kids whose neighborhoods are unsafe and drug infested (*Wall Street Journal*. March 25, 1991: A-1). Their parents are often poor and single. It would be nice if those children had more recreational and educational options, but the reality is that they frequently do not.

As they grow up, our children must adjust to the electronic age and put TV into reasonable perspective. We must teach them this without simply turning off the TV. My experience with my three teenaged daughters has been that they tend to watch TV when there seems to be nothing better to do; they much prefer socializing with their friends, shopping, and engaging in more active pursuits. Also, their taste in music is not Brahms, which would put them to sleep when they do their homework. They prefer the Hot 30 Countdown, featuring Timmy T; Tara Kemp; Escape Club; Styx; and Jellyfish (DP).

MAX BADER, MD
2 SW Del Prado
Lake Oswego, OR 97035

1. Stiehm ER. Your child's best friend: TV or not TV? *AJDC*. 1991;145:257.

In Reply.—I agree with Dr Bader that there are worthwhile things on TV and that monitored, selective viewing is harmless, amusing, and sometimes educational. Such monitored viewing did not work at our house; nor, I daresay, does it work in most houses, so the choice is no monitoring or no TV.

For the alcoholic, abstinence is necessary; for the nonalcoholic, ab-

stinence is harmless. I have yet to see any adverse emotional, social, or physical consequences of "hypotelevisemia." Has anyone?

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Misdiagnosis of Reye's-like Illness

Sir.—There are a number of case reports in the literature describing children with inborn errors of metabolism who have previously been misdiagnosed as having Reye's syndrome.^{1,4} It is not known, however, whether these cases represent rare events or whether the misdiagnosis of Reye's syndrome is common in clinical practice.

We previously reported⁵ the results of an epidemiologic study in which we demonstrated that the association between Reye's syndrome and prior exposure to aspirin was not accounted for by bias. In that study, potential cases of Reye's syndrome were reported to the investigators from a network of 108 pediatric tertiary care centers throughout the United States and Canada. The purpose of the present report is to describe the potential for misdiagnosis of Reye's syndrome in clinical practice by comparing the final diagnoses made by physicians who cared for the patients with the diagnoses made by a panel of three physicians with extensive knowledge and expertise in Reye's syndrome. We also investigated whether the age of the patient, the severity of the illness, and a history of aspirin exposure might contribute to the misdiagnosis of Reye's syndrome.

The results of liver biopsies are often accepted as conclusive evidence in either confirming or excluding the diagnosis of Reye's syndrome.⁶ However, abnormalities demonstrated by light microscopy are not specific to Reye's syndrome and cannot be relied on to confirm the diagnosis.^{7,8} Electron microscopy is now widely recommended to confirm the diagnosis, although, to our knowledge, no one has reported on the va-

lidity or reliability of this technique as it is used in clinical practice.

Research Methods.—**IDENTIFICATION AND ENROLLMENT OF SUBJECTS.**—Between January 1986 and July 1987, surveillance clinicians at each of 108 hospitals were asked to notify the researchers as soon as a patient was admitted for whom the diagnosis of Reye's syndrome could be considered, even if the diagnosis had already been ruled out. Subjects were ineligible if they had a history of Reye's syndrome, chronic liver disease, chronic encephalopathy, or a chronic disorder for which salicylates or acetaminophen were strongly indicated or contraindicated (eg, juvenile rheumatoid arthritis). After receiving reports of potential subjects, physician-researchers (B.W.F., R.I.H., and E.D.S.), blind to the medication history of the subject, decided on eligibility using predetermined guidelines. The guidelines had two purposes. The first was to allow for the early exclusion of children for whom there were already sufficient data to rule out conclusively the diagnosis of Reye's syndrome (eg, normal aminotransferase and ammonia levels). Second, the guidelines were intended to ensure that children were enrolled whenever there was any possibility that they might have Reye's syndrome.

DIAGNOSTIC CLASSIFICATION.—The "hospital diagnosis" was recorded as the discharge diagnosis on the hospital discharge summary sheet. This diagnosis was categorized as either definite Reye's syndrome, uncertain Reye's syndrome, or definitely not Reye's syndrome. The uncertain category included those cases in which terms were used that suggested uncertainty, such as "possible Reye's syndrome," and indeterminate expressions, such as "rule out Reye's syndrome." The category "definitely not" Reye's syndrome included those patients for whom an alternative diagnosis was recognized.

Three physicians who have extensive research experience and clinical expertise in Reye's syndrome were chosen to form an expert panel. The panel reviewed all data from each subject. These included a

Table 1.—Agreement Between Diagnoses of Reye's Syndrome by Hospital Physicians and Expert Panel*

Hospital Physicians	Expert Panel			Total
	Definite	Uncertain	Definitely Not	
Definite	22	7	5	34
Uncertain	2	7	4	13
Definitely not	1	5	10	16
Total	25	19	19	63

*Overall agreement equals 62% (39 of 63 patients). $\kappa_w = .48$.

copy of the complete hospital record and a detailed account of the illness prior to hospitalization obtained through interviews of all persons who had cared for the child. The panel then assigned each subject to one of the three categories described above. Individual judgments were made by panel members before a consensus was reached. All references in the records to medications administered before hospitalization were removed before review.

The stage of severity of Reye's syndrome was classified according to the criteria developed by the National Institutes of Health Consensus Conference on Reye's syndrome: stage 1 includes children with lethargy, and stage 2 requires evidence of combative behavior or delirium. Stages 3 through 5 include coma with increasingly severe neurologic deficits.⁹

REVIEW OF ELECTRON MICROGRAPHS OF LIVER BIOPSY SPECIMENS.—Whenever electron micrographs of liver biopsy specimens were available, copies were reviewed by John Partin, MD, a member of the panel and an authority on abnormalities of liver ultrastructure in Reye's syndrome.^{6,10} The results of these reviews were made available to the panel before they reached their consensus.

METHODS OF ANALYSIS.—The extent of agreement between the expert panel and the hospital physicians was assessed using the percentage of observed agreement. We also calculated a weighted κ statistic (κ_w) to correct for chance agreement. Individual weights were assigned as follows: 1 for complete agreement between the hospital discharge diagnosis and the consensus of the expert panel; $\frac{1}{2}$ for a disagreement that is one category apart; and 0 for a disagreement that is two categories apart. The value of κ_w can vary from +1, indicating perfect agreement, to 0, indicating no better than chance agreement. The κ_w value was interpreted as follows: when the value of the index was less than .4, the rating of agreement was poor; when the index was between .4 and .59, the rating was fair; when the index was between .60 and 0.75, the rating was good; and when the index was greater

Table 2.—Agreement Between Diagnoses of Reye's Syndrome by Hospital Physicians and Expert Panel for Different Age Groups

Hospital Physicians	Expert Panel					
	Patient Age ≤ 3 y*			Patient Age > 3 y†		
	Definite	Uncertain	Definitely Not	Definite	Uncertain	Definitely Not
Definite	2	6	3	20	1	2
Uncertain	0	3	2	2	4	2
Definitely not	0	3	7	1	2	3

*Overall agreement equals 46% (12 of 26 patients). $\kappa_w = .29$.

†Overall agreement equals 73% (27 of 37 patients). $\kappa_w = .54$.

than .75, the rating of agreement was excellent.¹¹

Results.—One hundred twenty-nine patients who met the eligibility criteria were reported to the investigators. Of these, 63 patients fulfilled the screening criteria as candidate case subjects, and complete data about them were obtained. These 63 patients were from 46 medical centers: 34 centers reported one case only, nine centers reported two cases, and three centers reported three or more cases. Nineteen subjects (30%) were classified as having stage 1 severity; 17 (27%) had stage 2; and 27 (43%) had stage 3 or greater.

COMPARISON OF HOSPITAL DIAGNOSES WITH DIAGNOSES OF EXPERT PANEL.—The comparison between the final diagnoses made by hospital physicians and the diagnoses made by the expert panel are shown in Table 1. The panel confirmed the diagnosis of definite Reye's syndrome in only 22 (65%) of the 34 hospital-diagnosed cases, and made the diagnosis of definite Reye's syndrome in three other cases not considered to be definite Reye's syndrome by the hospital physicians. Only 10 (53%) of the 19 subjects considered by the expert panel to definitely not have Reye's syndrome had been similarly classified by the hospital physicians. Overall agreement was 62% and κ_w was .48, indicating only fair agreement.

Substantial differences in levels of agreement existed between the expert panel and hospital physicians depending on whether the child was aged 3 years or younger (26 subjects) or older than age 3 years (37 subjects) (Table 2). For the younger children, the overall agreement rate was only 47% ($\kappa_w = .29$); for the older children, the overall agreement rate was 73%

($\kappa_w = .54$). The expert panel confirmed the diagnosis for only two (18%) of the 11 younger children compared with 20 (87%) of the 23 older children diagnosed by the hospital as having definite Reye's syndrome ($\chi^2 = 15.41$; $P < .0001$).

As might be expected, there was less agreement between the hospital physicians and the expert panel for those children classified as having stage 1 disease severity (overall agreement, 53% [10 of 19 patients]; $\kappa_w = .23$) than for those children in stage 2 (overall agreement, 76% [13 of 17 patients]; $\kappa_w = .66$), or stage 3 and greater (overall agreement, 59% [16 of 27 patients]; $\kappa_w = .43$).

Hospital physicians often made the diagnosis of definite Reye's syndrome even when a child had not received aspirin: 11 (33%) of the 33 subjects who did not receive aspirin were considered to have definite Reye's syndrome by the physicians who cared for them at the hospital. However, in only two (18%) of these 11 cases was the diagnosis confirmed by the expert panel who were blind to information about exposure to aspirin.

USE OF LIVER BIOPSY SPECIMENS AND COMPARISON OF RESULTS WITH EXPERTS' REVIEW.—Liver biopsies were performed on 13 subjects and postmortem liver specimens were available for five other patients. Biopsies were performed no more frequently for those children aged 3 years or younger than for those children older than 3 years (31% vs 27%). Electron microscopy was performed on 14 specimens and photomicrographs of 13 of these specimens were available for review by the expert physician. Of the seven cases considered by hospital pathologists to be diagnostic of Reye's syndrome, only

two were considered diagnostic by the experts; two others were questionable, and three were considered inconsistent with Reye's syndrome. Overall agreement was only 46%, and κ_w was .27, indicating poor agreement.

Comment.—The results of this study demonstrate that a diagnosis of Reye's syndrome in pediatric tertiary care hospitals was often not confirmed when the data were reviewed by a panel of experts. One third of cases were considered by an expert panel to be misdiagnosed. The study was performed between 1986 and 1987 when the incidence of Reye's syndrome was declining. As the incidence of true cases of Reye's syndrome declines further, a greater proportion of those patients given the diagnosis will likely be misdiagnosed.

Of the 12 patients considered to have false-positive diagnoses, nine were younger than age 3 years. The reluctance of the expert panel to make the diagnosis of Reye's syndrome in a young child is almost certainly due to their concern that inborn errors of metabolism had not been excluded as an alternative diagnosis. At the same time, in only one (2%) of the 63 subjects was a definitive diagnosis of an inborn error of metabolism made, and in only five (19%) of the 26 children aged 3 years or younger were investigations requested that were specific for these disorders. It appears from these data that the warnings to clinicians to consider the possibility of inborn errors of metabolism when faced with a young child with a Reye's-like illness are going largely unheeded.

Even as the incidence of Reye's syndrome declines, physicians need

to be careful that children who present with a Reye's-like illness are not misdiagnosed. Young children, in particular, may require biochemical investigations for inborn errors of metabolism, and a liver biopsy may be indicated. In addition, review of the biopsy specimen by someone who is experienced in interpreting electron micrographs in patients with Reye's syndrome may help to avoid misdiagnoses.

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This research was supported in part by the American Home Products Corp, Bristol-Myers Co, and Sterling Drug Co, New York, NY; Miles Laboratories Inc, West Haven, Conn; and Procter and Gamble Co, Cincinnati, Ohio.

The authors have no ongoing affiliation or financial involvement with any of these companies or with any other organization or entity with a direct financial interest in the subject matter or material of the research discussed in this letter.

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Syringomas in Down Syndrome

Sir.—Syringomas are small, skin-colored or slightly yellow, firm papules that frequently appear in crops and are usually located in the periorbital area (Figure). They may also appear on the side of the neck, cheeks, thorax, abdomen, axilla, and pubic area. An association between syringoma syndrome (DS) and syringomas was first reported by Butterworth et al¹ in 1964. They studied a residential population whose ages ranged from 10 to 52 years; the majority of the patients were adults. The incidence of syringomas in the population with DS was 18.5%, with 26% of the women and 13% of the men having syringomas. The comparison group, 1001 mentally retarded individuals without DS, had a 0.6% incidence of syringomas. Another study in 1976,² also of institutionalized residents with DS, reported an incidence of syringomas in 26.6% of the male and 58.1% of the female subjects. There are no reports concern-



Syringomas seen in child with Down syndrome.

ing the association of DS and syringomas in a younger population.

Patients and Methods.—In an attempt to confirm the results of previous studies, but in a younger population, 32 patients with DS between ages 14 and 25 years who were being seen for routine follow-up in our DS clinic were evaluated for facial syringomas. Because syringomas usually do not appear before puberty, only patients with DS aged 14 years or older were included in the study. These patients were followed up for an average of 13 years. A comparison group of 50 children without DS with and without mental retardation and matched for age was examined for the presence of syringomas. The syringomas in both groups were restricted to the face.

Results.—Fifteen (46.9%) of the 32 patients with DS examined had syringomas. The majority of patients studied (62.5%) were in the 14- to 20-year age group and 21 (65.6%) of the 32 patients were men. Eight (38%) of the men and seven (63.6%) of the women had syringomas. Patients with syringomas did not have a greater incidence of congenital heart disease, hypothyroidism, or other abnormalities associated with DS than the group with DS without syringomas, although one did have diabetes mellitus. One of the 50 patients of the control group matched for age (a patient with Williams syndrome) had facial syringomas.

Comment.—The results of this study substantiate the findings of two prior reports concerning an association of syringomas with DS. The rate of occurrence in our patients was higher than anticipated because of the preponderance of men and younger individuals in our study group (syringomas appear more commonly in women and older individuals). How-

ever, this may be spuriously high due to the relatively small number of patients in the study group.

Syringomas were first described by Kaposi in 1876. They are uncommon, appear usually during puberty, and have been reported to occur in families. They are usually 1 to 3 mm in diameter but can be larger. Syringomas are benign, and there are no reports of them undergoing malignant degeneration. Histologic, histochemical, and electron microscopic findings show a close relationship between syringomas and intraepithelial eccrine sweat gland ducts. Brownstein³ described syringomas as adenomas of the intraepidermal portions of the eccrine duct. Small cystic ducts as well as solid epithelial strands embedded in fibrous stromas are seen on histologic examination of the upper and middle area of the dermis.

Syringomas may be mistaken for xanthomas because of their location around the eyes. However, xanthomas are somewhat larger and yellowish in color, while syringomas have a flesh-like or light yellow color.

Treatment is usually not necessary except for cosmetic reasons. Isotretinoin has recently been used to treat syringomas, but it is not recommended for routine treatment because of the benign nature of these skin lesions and the possible risks of the medication.⁴

The association of syringomas and DS has not previously been reported in the pediatric literature. It is important for pediatricians to be aware of the significance of syringomas in patients with DS so that they can inform the patient and family of the benign nature of these lesions and not subject the patient to an unnecessary evaluation.

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This study was supported by a grant from the Genesis Fund.

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Congenital Syphilis Associated With Negative Results of Maternal Serologic Tests at Delivery

Sir.—The incidence of congenital syphilis has steadily increased in the last decade. In 1988, 691 cases of early congenital syphilis were reported to the Centers for Disease Control.¹ This is the largest number of cases reported to the centers since the early 1950s, when penicillin became widely used to treat syphilis in pregnant women.¹ Because congenital syphilis generally can be prevented by detection and treatment of syphilis early in pregnancy, failure to obtain adequate prenatal care is believed to be the most important factor associated with congenital syphilis.^{1,2}

Current recommendations from the Centers for Disease Control require that all states perform serologic screening tests for detecting syphilis at the beginning of prenatal care. Additional screenings at the beginning of the third trimester (28 weeks) and at delivery also are recommended for mothers who live in areas with high incidences of syphilis.²⁻⁴ This approach will reveal almost all cases of antepartum infection. However, it may not detect infection acquired immediately before delivery when results of serologic tests may be negative.³⁻¹⁰ We describe three infants born to mothers with peripartum syphilis that was not diagnosed by routine serologic screening at delivery. Two mothers were seronegative at delivery, but their infants later developed evidence of congenital syphilis. The third infant was born to a seronegative mother with primary syphilis diagnosed post partum; this infant was asymptomatic and received prophylactic antimicrobial therapy after delivery. These cases underscore the limitations of current prenatal screening methods.

Patient Reports.—PATIENT 1.—A 2385-g male was delivered vaginally at 36 weeks' gestation to a 20-year-old black woman. The pregnancy was uncomplicated and the result of a maternal rapid plasma reagin (RPR) test did not show reactivity at delivery. No maternal genital lesions were noted. Results of physical examination of the infant were normal, and he and his mother were discharged from the hospital. Two months after delivery, the mother was diagnosed with salpingitis due to *Neisseria gonorrhoeae* and received ceftriaxone sodium and doxycycline-hydrate. No genital lesions were noted; a serologic test to detect syphilis was not performed at that time.

The infant was in good health until age 2½ months, when he developed clear rhinorrhea and a generalized maculopapular rash with oval red lesions and superficial desquamation. On presentation at the emergency department, hepatosplenomegaly and axillary adenopathy were noted. Roentgenograms of the long bones revealed symmetric osteochondritis and periostitis. Laboratory evaluation revealed a hemoglobin level of 90 g/L, hematocrit of 0.27, and a platelet count of $422 \times 10^9/L$. The alanine aminotransferase, aspartate aminotransferase, and γ -glutamyltransferase (GGT) levels were 65, 140, and 128 U/L, respectively. The total bilirubin level was 6 $\mu\text{mol/L}$. The serum VDRL titer was 1:128, and the result of the microhemagglutination assay to detect *Treponema pallidum* (MHA-TP) antibody showed reactivity. Laboratory test results of the infant's cerebrospinal fluid showed no white blood cells and normal glucose and protein concentrations. The cerebrospinal fluid was nonreactive during VDRL testing. The IgM reactivity of whole serum with *T pallidum* antigens was examined using Western blotting¹¹; an IgM response to *T pallidum* antigens with apparent molecular masses of 47, 45, and 17 kd was observed. The infant was diagnosed as having congenital syphilis and received 200 000 U/kg of intravenous penicillin G daily for 10 days. There was no history or physical signs of sexual abuse.

The mother's VDRL titer was 1:8, and the result of an MHA-TP assay showed reactivity. Antibody to the human immunodeficiency virus (HIV) was not detected. She was diagnosed as having early latent syphilis and was treated with 2.4 million U of benzathine penicillin G intramuscularly.

PATIENT 2.—A 3550-g female was delivered vaginally at 40 weeks' gestation to a 20-year-old black woman following an uncomplicated pregnancy. The result of a maternal RPR test at delivery did not show reactivity, and there were no signs of 1° or 2° syphilis. Results of physical examination of the newborn were normal.

At age 2 months, the infant appeared to experience pain when lifted at the shoulders, and subsequently the parents noted decreased movement of the left arm. The infant was taken to the emergency department for evaluation. Roentgenograms of the long bones revealed symmetric osteochondritis and periostitis of the upper and lower extremities and osseous destruction of the proximal medial tibial metaphysis (Wimberger's sign). There was no associated rash or hepatosplenomegaly; bilateral axillary lymphadenopathy was present. Laboratory evaluation revealed a hemoglobin level of 80 g/L, hematocrit of 0.25, reticulocyte count of 34×10^{-3} , and a platelet count of 724×10^9 /L. Results of liver function tests were normal. The serum VDRL titer was 1:128, and the result of the MHA-TP assay showed reactivity. Examination of the cerebrospinal fluid revealed the following values: red blood cell count, 16×10^6 /L; white blood cell count, 25×10^6 /L (0.24 mononuclear, 0.69 lymphocytes, and 0.07 segmented cells); and a protein level of 0.51 g/L. The result of a VDRL test did not show reactivity. The infant was hospitalized and diagnosed as having congenital syphilis. She was treated with 150 000 U/kg of intravenous penicillin G daily. A dose of 37 500 U/kg was administered every 6 hours for 10 days. Western blot analysis¹¹ revealed serum IgM reactivity with the 47- and 45-kd antigens of *T pallidum*. There was no evidence of physical or sexual abuse.

The mother's VDRL titer was 1:512; the result of an MHA-TP assay did not show reactivity. She had palmar and plantar rashes consistent with secondary syphilis and received 2.4 million U of benzathine penicillin G. She lacked antibody to HIV.

PATIENT 3.—A 2550-g female was delivered vaginally at 36 weeks' gestation to a 28-year-old black woman who had received no prenatal care. The result of an RPR test of the mother at delivery did not show reactivity. However, on the second day after delivery, an ulcerated perineal lesion was noted that contained motile spirochetes detected with darkfield microscopy. The result of an MHA-TP assay did not show reactivity. The mother's serum did not exhibit a prozone reaction; diluted serum was nonreactive during VDRL testing. She was diagnosed as having primary syphilis and was treated with 2.4 million U of benzathine penicillin G intramuscularly. The result of a test to detect antibody to HIV was negative. Results of physical examination of the infant were normal. Roentgenograms of the long bones and results of complete blood cell count and liver function tests were also normal. The result of a VDRL test performed on umbilical-cord blood did not show reactivity. No specific fetal IgM antibody to *T pallidum* antigens in

whole serum was detected using Western blot analysis.¹¹ The infant received an intramuscular injection of benzathine penicillin G (50 000 U/kg).

Comment.—Routine serologic testing of mothers during pregnancy and at delivery is essential to prevent congenital syphilis.² However, limitations on the usefulness and reliability of such screening tests exist. Serologic tests are poor diagnostic tools during the incubation or early primary stage of syphilis. During those times, results of the nontreponemal (RPR or VDRL) tests may not show reactivity because reactivity occurs approximately 4 to 8 weeks after the infection is acquired and several days to 1 week after the development of a chancre.^{10,12} In primary syphilis, nonreactivity to nontreponemal tests is reported to occur in approximately one fourth to one third of cases.^{5,8} Nonreactivity during the MHA-TP assay and the fluorescent treponemal antibody absorption test occurs in as many as 36% and 18% of cases of primary syphilis, respectively.⁹ It is clear that no single test or combination of tests will detect all cases of maternal syphilis and prevent neonatal infection. Our cases highlight these limitations, which are due to the natural history of the development of clinical signs of syphilis and production of antibody to that infection. As shown in the mothers of patients 1 and 2, the mother may transmit infection to the fetus during the period of seronegativity in early primary or incubating syphilis. The importance of diligent physical examination to detect suspicious lesions supplemented by darkfield or immunofluorescence microscopic¹³ examination in the diagnosis of primary syphilis is demonstrated in the mother of patient 3.

Another possible explanation for the nonreactivity during nontreponemal tests is the prozone phenomenon.^{5,8,12} Less than 2% of serum samples from patients with secondary syphilis will exhibit a prozone effect.^{5,8,12} This phenomenon is due to excess reagin antibody, which prevents flocculation in the undiluted serum sample. When diluted, the serum will usually exhibit titers of 1:16 or greater. The prozone reaction was not specifically sought in serum samples from the mothers of patients 1 and 2. It is unlikely, however, that

it contributed to the nonreactivity during nontreponemal testing in our patients. Serum exhibiting a prozone phenomenon will show a nonreactive, rough appearance or be weakly reactive during nontreponemal testing.⁸ Serum samples with such equivocal reactions are diluted routinely in our laboratory and, if the prozone effect were present, it would have been detected in our patients.

There was no history or physical evidence of sexual abuse in patients 1 and 2. Moreover, syphilitic osteochondritis and periostitis require approximately 5 and 16 weeks, respectively, to become demonstrable on long bone roentgenograms.¹⁴ This period is consistent with perinatal acquisition of *T pallidum* in both infants.

With the dramatic increase in the incidence of congenital syphilis, areas with a high prevalence of infectious syphilis in women of childbearing age may need to screen women post partum to detect prior incubating or seronegative primary infection at delivery. Moreover, if a woman with a child younger than 1 year is diagnosed to have primary, secondary, or early latent syphilis, that child should be fully evaluated for signs of congenital syphilis, tested serologically, and treated accordingly. When a woman is treated for late syphilis, all of her young children should also be evaluated. Only with adequate prenatal care and postpartum evaluation will congenital syphilis be prevented.

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We thank the staff of the Immunology Laboratory of Parkland Memorial Hospital, Dallas, Tex, for assisting in handling specimens and performing serologic testing and the Transfusion Service staff of PMH for assistance in collection of umbilical-cord blood specimens.

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Response of Seronegative Adults to Measles Immunization

Sir.—In March 1990 we published a study in *AJDC*¹ indicating that adult hospital employees, with significant frequency, tested seronegative to measles. We identified 16 such workers whom we subsequently immunized with monovalent measles vaccine. We further recommended and initiated a screening program to test new employees for immunity to measles and to immunize those who tested seronegative.

Correspondents have suggested to us that these seronegative individuals might represent primary immunization failures, and, therefore, a significant number might not seroconvert following the administration of vaccine. Some expressed interest in follow-up data on this population.

Accordingly, we solicited and were able to obtain serum samples from 15 seronegative individuals and study them by the methods described in our article.¹ Of these 15 employees who were subsequently vaccinated, 13 were members of the original group of 16 and two were employees identified in our ongoing screening program.

All 15 employees tested developed immunity to measles following vaccination. These data suggest that seronegative adults do not represent individuals who fail to respond to measles vaccination. Although the group we studied was small, their response to vaccination does not appear to differ significantly from that of the population at large.²

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Improvement of Leukemic Hyperleukocytosis With Only Fluid and Allopurinol Therapy

Sir.—Children with leukemic hyperleukocytosis ($>100 \times 10^9/L$) may have manifestations of hyperviscosity with disseminated intravascular coagulation, intracranial hemorrhage, and pulmonary insufficiency as well as the tumor lysis syndrome.¹ Initial treatment before chemotherapy includes vigorous intravenous fluid therapy, allopurinol, and intrave-

nous sodium bicarbonate to decrease the risk of uric acid nephropathy. Some patients have received leukapheresis, exchange transfusion, or cranial irradiation to treat or prevent the manifestations of hyperviscosity.¹⁻⁵ A current protocol recommends leukapheresis or exchange transfusion if the cytocrit (volume of packed red blood cells and volume of packed white blood cells) is greater than 0.30.⁶

Three patients had a marked drop (52% to 89%) in leukocyte count during 1 to 2 days while receiving intravenous hydration, sodium bicarbonate, and allopurinol therapy and before receiving any chemotherapy. Thus, the more aggressive measures may be avoided in some patients who have no symptoms of hyperviscosity and whose leukocyte counts decrease to levels at which there is no longer a concern about hyperviscosity.

Patient Reports.—Data from the three patients are outlined in the Table. No patient had any manifestations of the hyperviscosity syndrome and no child was clinically dehydrated or had laboratory evidence of dehydration as assessed by tests of urine specific gravity and blood urea nitrogen. The liver and spleen in patient 1 were palpable 7 cm below the costal margins; the spleen in patient 2 was palpated down to the umbilicus, and the liver was not enlarged; and the liver and spleen in patient 3 were palpated down 6 and 4 cm, respectively.

The uric acid and creatinine levels were normal and remained normal during the hydration period. Only patient 1 had a cytocrit determination (0.20). Manual counts were done when the leukocyte count was greater than $100 \times 10^9/L$, and immunologic typing and cytochemistry confirmed the type of leukemia. All patients were treated with Children's Cancer Study Group protocols. Patient 1 received an autologous transplant and 8 months later was free of disease; patient 2 received treatment for 3 years and has not been receiving treatment for 1 year; and patient 3 remained in remission 5 months after she completed 2 years of chemotherapy.

Comment.—The observation of a significant decrease in the leukocyte count in children with leukemia shortly after admission and before receiving chemotherapy has been observed by others but not documented in the literature, to my knowledge.^{7,8} The changes were attributed to the stress of hospitalization and the resulting secretion of corticosteroids.

THE PEDIATRIC FORUM

Patient Data									
Patient No./ Age	Type of Leukemia	Initial		Interval Between Fluid Administration, h	After Hydration		Decrease in WBC Count, %	Hemoglobin, g/L	Platelets, $\times 10^9/L$
		WBC Count, $\times 10^9/L$	Blasts		WBC Count, $\times 10^9/L$	Blasts			
1/5 mo	AML	129	0.74	18	62.4	0.68	52	40	61
2/5 mo	ALL	572	0.80	32	179	0.74	69	90	78
3/3.5 y	ALL	121	0.86	50	16.3	0.45	89	60	18

*AML indicates acute myelocytic leukemia; ALL, acute lymphocytic leukemia; and WBC, white blood cell.

Some children with acute lymphocytic leukemia are exquisitely sensitive to small doses of corticosteroids, and this theory is perhaps plausible. It would not, however, explain the 52% decrease in leukocyte count of patient 1 who had acute myelocytic leukemia. Such marked sensitivity to corticosteroids would be most unusual in that form of leukemia.

The infrequent temporary remissions following blood transfusions have also been attributed to a stress reaction.⁷ Two of the three patients (patients 1 and 3) received packed red blood cells during the hydration period, but I believe that this is an unlikely explanation. Only patient 3 had evidence of infection (sepsis) that could also be associated with temporary remissions.⁹ No antileukemic effect has ever been attributed to allopurinol, sodium bicarbonate, or intravenous fluids, to my knowledge.

It is not known whether the decreases in leukocyte count reflect an actual decrease in leukemic cell mass or are only the result of redistribution, ie, into the marginal leukocyte pool, spleen, or liver. The three patients had very large spleens and, conceivably, expansion of the blood volume with intravenous fluids may have increased the circulation in the enlarged spleens, resulting in increased sequestration of the leukemic cells. Marginal pools have not been studied in leukemic patients, to my knowledge, but it seems unlikely that this explains the shifts of the magnitude observed in these patients.

Allopurinol is a xanthine oxidase inhibitor that reduces the production of uric acid by inhibiting the biochemical reactions immediately preceding its formation. It acts on purine catabolism without disrupting the biosynthesis of purines and has no known antileukemic effect. The absence of

an elevated uric acid level during the hydration period does not rule out leukemic cell destruction since the patients were receiving allopurinol and sodium bicarbonate to decrease the risk of uric acid nephropathy.

Thus, there appears to be no obvious explanation for this phenomenon, but it does occur in some patients and has clinical relevance. I suggest that a 24- to 48-hour regimen of intravenous fluid, allopurinol, and sodium bicarbonate be administered to a child with leukemic hyperleukocytosis who has no signs or symptoms of hyperviscosity. Following this trial, a decision could be made about whether more aggressive measures, ie, exchange transfusion or leukapheresis, are necessary depending on the change in leukocyte count or the development of manifestations of hyperviscosity. The decreased viscosity associated with anemia often helps to compensate for the increased viscosity due to the hyperleukocytosis; therefore, blood transfusions should be avoided, if possible.¹⁰

It should be noted that in a series of 124 children with acute lymphoblastic leukemia and leukocyte counts greater than $200 \times 10^9/L$, the incidence of intracranial hemorrhage was only 3% and hemorrhages in three of the four patients occurred before presentation.¹ Patients who present with symptoms of hyperviscosity should be treated with exchange transfusion or leukapheresis to immediately correct the hyperviscosity. Further studies would help to verify these changes in leukocyte counts before chemotherapy and to explain the mechanism.

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Myopathy Associated With Ketoconazole Treatment

Sir.—Ketoconazole is an imidazole-derivative, broad-spectrum antimycotic agent, with relatively limited

toxicity compared with other antifungal medications. However, gastrointestinal disturbances, hepatotoxicity, impaired adrenal steroidogenesis, gynecomastia, and immune hemolytic anemia have been reported in association with ketoconazole treatment.^{1,2} We noticed myopathy with a significant increase of serum creatine phosphokinase during ketoconazole treatment, indicating a possible drug-induced myositis. To our knowledge, there has been no fully documented report of myopathy associated with the use of this drug, although myalgia has been reported in two patients³ and muscular weakness in one patient.⁴

Patient Report.—A 17-year-old boy afflicted with autoimmune polyglandular syndrome type I presented with hypoparathyroidism, Addison's disease, alopecia universalis, and mucocutaneous candidiasis was treated with ketoconazole (200 mg/d) because of worsening oral candidiasis. Within a week, doctors noticed clinical improvement of the oral lesions, but concomitantly, the patient developed significant weakness and diffuse myalgia, particularly of the shoulder girdle muscles. The serum creatine phosphokinase level, which had been normal 2 months earlier, rose to 5200 U/L (normal range, 24 to 200 U/L), and of this, 96% was isoenzyme of skeletal muscle origin. Liver enzyme levels remained unchanged, serum electrolyte levels were normal, and no antiskeletal muscle antibodies were found. The electrocardiogram was normal, but the electromyogram revealed a distinct myopathic pattern. Ketoconazole therapy was discontinued 8 days after its start, and rapid clinical improvement followed with eventual disappearance of myalgia and weakness. One week after withdrawal of the drug therapy, the serum creatine phosphokinase level had decreased to 480 U/L, and after 3 weeks to 96 U/L. Repeated electromyogram obtained 5 weeks after withdrawal of ketoconazole therapy was normal; viral cultures were negative. Results of serologic tests for influenza A, influenza B, adenovirus, enterovirus, cytomegalovirus, herpesvirus, hepatitis A virus, hepatitis B virus, Epstein-Barr virus, mycoplasma, streptococci, and *Toxoplasma* remained unchanged.

Results of a macrophage inhibiting factor test⁵ for ketoconazole were negative, and results of a mast cell degranulation test⁶ for ketoconazole were positive, indicating the possible presence of IgE antibodies to the drug. However, the relationship of this finding to the myositis is questionable.

Comment.—There have been reports of myositis or myasthenia in

patients with mucocutaneous candidiasis, but these cases were usually associated with long-standing muscle disease or thymoma.⁷ Chest roentgenography failed to show an enlarged thymus in our patient. Moreover, the temporary relationship between clinical symptoms and laboratory evidence of myositis shortly after the start of ketoconazole treatment, and their rapid resolution after discontinuation of this medication, suggest a drug-related myopathy.

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Gallstones in Children

Sir.—Recently, Reif et al¹ described 50 children and adolescents with gallstones and discussed the conditions associated with the development of gallstones in children, with the exception of erythropoietic protoporphyria (EPP). Of the two most common porphyrias, EPP rivals porphyria cutanea tarda in prevalence,

and is characterized clinically by photosensitivity commencing in childhood and biochemically by excessive amounts of red blood cell protoporphyrins.² Protoporphyrin is excreted in the bile and gallstones, which are partially composed of protoporphyrin and have been reported in about 12% of patients with EPP who are liable to produce symptoms at an unusually early age.³ Determination of the protoporphyrin solubility in the bile and the mechanism by which gallstones form in patients with EPP is poorly understood. Results of scientific research on rat models have shown that biliary protoporphyrin excretion depends on bile acids and, if bile acid excretion rates decrease, biliary concentration of protoporphyrin increases, which may predispose to gallstones.⁴

Ten of the 50 patients described by Reif et al had no associated conditions, and their disease was categorized as idiopathic. Patients with EPP may experience photosensitivity without any objective physical signs; if their complaint is initially dismissed by their family physician, they may fail to mention it to future physicians.⁵ It is important not to miss the diagnosis of EPP because a number of patients may develop fatal liver disease and there is evidence that early detection can improve the outcome.⁶ Therefore, I suggest that a medical history should be taken for photosensitivity for those children with idiopathic gallstones; if present, red blood cell protoporphyrin levels should be determined. If cholecystectomy is performed, sections of the gallstones can also be examined with fluorescence microscopy to detect protoporphyrins.⁷

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Obesity and Body-Mass Index

Sir.—The discussion on the percentile curves of body-mass index (BMI) by Hammer et al¹ alerts the pediatrician to another method of getting more involved in clinical nutrition. Pediatricians see a significant amount of nutritional problems, especially obesity, and can apply these curves to help improve the patient's weight per height. However, the authors hedge on the diagnosis of obesity by saying "... we have found the 95th percentile BMI to be a conservative cutoff point for defining obesity in childhood." There are better criteria for defining obesity, especially for adolescents. These can be extracted from the National Center for Health Statistics² and were recently reprinted.³ Using these tables for ages 12 to 17 years, the ideal body weight can be estimated, and obesity can be defined as greater than 20% above the ideal body weight. We recommend that clinicians post these tables in their offices and refer to them when estimating the ideal body weight and percentile of ideal body weight.

With respect to estimation of body fat, skinfold measurements can be imprecise and inaccurate, but in trained hands, skinfold measurements can add an important step in assessing body fat. In 1988, Slaughter et al⁴ published equations for estimating the percentile of body fat in preteens and teenagers using two simple skinfold measurements with a standard error of about 3.8%. The

value of these equations is that they were established using a four-component model and represent the best method of computation available.

The BMI graphs and table provided by Hammer et al are an important step in getting the pediatrician to make a more accurate assessment of the patient's weight per height, and the authors should be congratulated in providing the pediatrician with a tool to get more involved in clinical nutrition. In addition, the tables for estimating the percentile of ideal body weight for the National Center for Health Statistics in using skinfold measurements and the equations developed by Slaughter et al might increase the pediatrician's skill in diagnosing obesity even further.

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In Reply.—We agree with Dr Hergenroeder's contention that pediatricians should become more involved in problems of clinical nutrition. In our article, we chose not to recommend a specific BMI or percentile of BMI as a criterion for the diagnosis of obesity. Until a level of BMI is identified that is either associated with an increase in morbidity, or predictive of later morbidity or mortality, the specification of a diagnostic cutoff point for obesity during childhood remains somewhat arbitrary.¹ Rather than emphasizing the diagnosis of

obesity, we recommend that clinicians use longitudinal assessments of BMI to monitor changes in weight relative to height and age, and that investigators continue to study the pattern of development of BMI and its relevance as a predictor of obesity. For example, Rolland-Cachera et al² have identified the timing of the adiposity rebound as a predictor of later obesity.

Further research is needed to demonstrate increased morbidity in association with either elevation of BMI, as identified for adults by the National Institute of Health Consensus Development Conference on Obesity (26.9 kg/m² for women and 27.2 kg/m² for men),³ or percentiles of BMI during childhood or adolescence.

Since BMI is influenced by lean and fat tissue, it should not be construed as a measure of fatness. Measurement of skinfold thickness provides an estimate of subcutaneous fat deposition, which is correlated with BMI.⁴ In those circumstances that require an estimate of body fatness, skinfold thickness or other indirect measures of fatness should be employed.

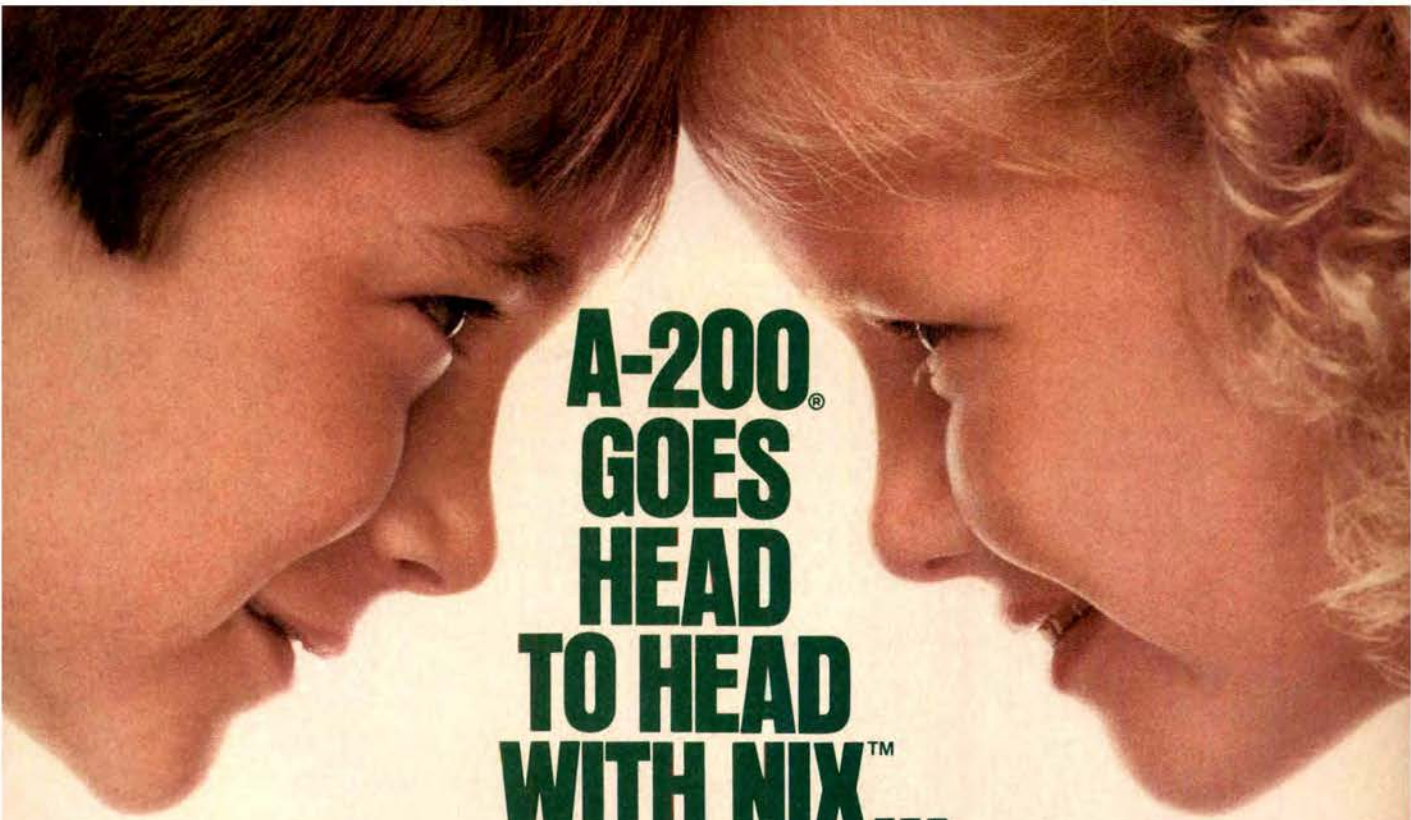
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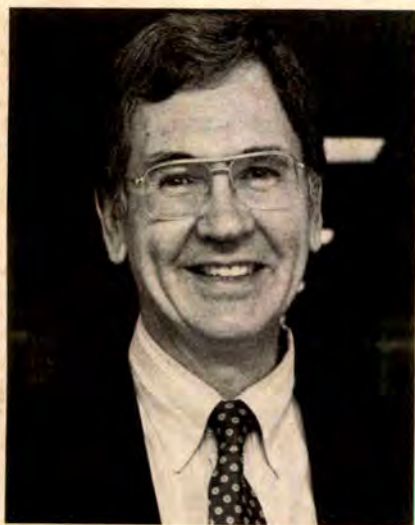
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The Clinic Attending: Teaching Strategies for Patient Encounters



Barton Schmitt, MD

Bart recently left the board after 10 years of dedicated effort. This contribution reflects his observations on an important academic function, appropriate teaching objectives for the instructor and learner.

Bart comes to this discipline with superb credentials. He has directed the General Consultative Services at the University of Colorado and Children's Hospital in Denver since 1986. He has also directed the telephone triage program since 1988, which enables the nursing staff in the emergency department to respond to parental inquiries. He also established a weekly conference series for practicing pediatricians that covers topics of direct applicability to office practice; the success of this venture is attested by the constant active attendance of between 40 and 50 community pediatricians.

*The second edition of his well-regarded book, **Your Child's Health**, will be distributed in September 1991, and in 1992, the second edition of his*

*text for providers, **Pediatric Telephone Advice**, will appear.*

Bart served AJDC extremely well in his decade of board membership. We shall miss his wisdom and participation.

—V.A.F.

Most of us in academic general pediatrics use continuity clinics, walk-in clinics, or emergency departments as our teaching turf. When I am working in these settings, my overriding goal is ensuring quality of care for all patients. My main educational goal is teaching residents how to think better about patient care. Knowing that we cannot teach everything in 3 years, I try to help residents approach problems in an organized and logical way that will provide a foundation for independent decision making. Here are some guidelines that help me fulfill my teaching responsibilities:

1. *Treat residents as adult learners:* Keep the learning environment respectful and nonthreatening. Challenge residents' thinking without challenging their status or self-esteem. Question learners to help themselves, not to reveal their uncertainties. Do not compete with residents, for they are the learners. Be open to disagreement. Never retaliate with verbal abuse of residents (eg, blaming, belittling, insulting, or demeaning comments).

2. *Use questions as the main vehicle for teaching:* The question-answer format is in contrast to the straight information giving, mini-lectures, or "this is what I would do" approaches. Questions stretch people. Questions help people crystallize and declare their position. Questions help people appreciate what they do know and do not know. Unless they

are encouraged to speak first, junior people may be intimidated by their senior colleagues. Some useful questions to stimulate discussion include the following: What do you think? How do you add it up? What is your differential diagnosis? Given this chief complaint, what is the one thing you must rule out (eg, epiglottitis in children with stridor)? What is your leading diagnosis? Is it confirmed or tentative? Which laboratory studies, if any, are indicated? Will the diagnosis or treatment be changed by the results? What is your treatment plan? What is your follow-up plan? How can we prevent recurrences?

3. *Encourage the resident to ask you questions:* If the diagnosis is straightforward (eg, conjunctivitis) and the resident has previous experience with the condition, bypass the usual case presentation and go directly to the resident's agenda or needs. If necessary, trigger this discussion with "How can I help you?" or "What are your questions?" Encourage the resident to clarify the information he or she needs to help the patient and to tap into the consultant's experience. The attending physician functions as a computerized encyclopedia of pediatrics. When residents ask questions, we should assume they do not know the answers, and we should answer them directly rather than countering with other questions. This approach is called resident-driven learning. As the clinic becomes busier, we can become more efficient by using this approach. Although teaching time decreases, teaching is never completely set aside.

4. *Recommend additional questions for the resident to ask the parent:* In patients with complicated symptoms (eg, chronic cough or syncope), the

database is often incomplete. Any unanswered questions that come up during the case discussion should be saved until later. The resident can then return to the parent and pursue these pertinent questions. Occasionally, the resident will be requested to perform an additional examination, such as a rectal or neurologic examination.

5. *See the resident's patients:* For medical liability and billing purposes, we need to see all patients. When the clinic is busy, however, we need to be selective about which patients we evaluate in depth. Anyone who has an unknown diagnosis or might be seriously ill needs our full attention. In addition, I perform a careful physical examination of any patient who might have a physical finding that could easily be missed by an inexperienced physician, eg, asymmetrical breath sounds with a foreign body, an enlarged spleen in a child with exudative tonsillitis, or an inflamed uvula in a child who is drooling.

6. *Bring the resident with you into the examining room:* Why this does not happen automatically, I am not certain. Some residents may believe they are already on top of everything and that we cannot add anything. However, if we are to teach by example, residents must be with us. In a way, they are right—we usually do not turn up a new physical finding—but we may trigger a line of questioning that leads to considering a new diagnosis (such as diarrhea from excessive consumption of pear juice, weight loss from an overly diluted formula, or passive smoking as a cause of out-of-control asthma). We can ask, "What are you most concerned about?" and more than 30% of the time we will turn up a "hidden agenda" that needs some education and reassurance. The nuances of obtaining medical histories could easily take an additional 3 years of training.

Other aspects of pediatrics that we can demonstrate are interactions with children: how to include them, interview them, put them at ease, or motivate them. We can show how to make the return visit easier by telling the fearful child how good he or she was following a painful procedure. There is always something to teach.

7. *Protect the resident's role as primary physician for this encounter:* One

of our goals is to help the resident treat patients independently. This is the role they have been studying for. We are the consultants for residents' cases. We do not replace residents unless we have their permission. If we agree with the residents' findings, we should commend them (eg, "good pick up") or concur with them ("I agree with your plan") in front of the parents. If we disagree, we should discuss our differences in the hallway. If they have never "defused" an angry parent, it may be more educational to "see one" before they "do one." The same holds true for removing a stubborn foreign body from the nose. However, if we rehearse appropriate advice with residents, they can provide the counseling (eg, for a colicky baby). Whenever we can talk a resident through the procedure, we should do so (eg, the reduction of a subluxed radius).

8. *Encourage the resident to convey all joint decisions to the parents:* Providing the parent with the diagnosis, treatment recommendations, and follow-up plan (ie, debriefing) is more complicated than obtaining the standard medical history and performing the physical examination. It requires a sensitivity to what the parent is able to understand and absorb. The parent needs an opportunity to respond to the advice. When time permits, try to observe this challenging part of the encounter. Also, encourage residents to give written information or instructions to parents. It can be handwritten, preprinted, or computer generated. Feedback about the resident's technique is helpful after the parent has departed (including interviewing skills).

9. *Encourage 5-minute reading breaks regarding disorders that are new to them:* The best learning combination is a patient with a disease the resident has not seen before, a knowledgeable attending physician, and a short article on the topic. Our learning curve peaks with a patient who needs our help. The new information is more likely to get into the permanent memory if the learner also reads a short description of the disease (eg, torticollis is just a few paragraphs in most texts). This is especially true for visual learners or people who mainly believe what they read. After the patient leaves and before the resident

becomes involved with another patient, we can direct him or her to a selected textbook or key article file. Reading about cases at the end of a long day is difficult.

10. *Bring all the residents in to see interesting physical findings:* This is one of the attending's responsibilities. We all like to say that we have seen "one of those" (eg, spider bite, labial adhesions, herpes whitlow, or urticaria pigmentosa). First, we need the parents' and patient's permission. Second, we need to round up the residents for a few minutes.

11. *Encourage 15-minute meal breaks, even if patients are waiting:* The statement, "We can't eat until everyone is seen" came from clinics that closed for lunch. If we are running an emergency department or walk-in clinic, we need to be sure our staff eats before the cafeteria closes. Some dedicated individuals (future victims of burnout?) actually need to be ordered to take a break. As long as all emergencies are handled, people should be sent for a quick bite to eat. Without food and fluids, residents lose efficiency, focus, judgment, and compassion. If the parents did not call for an appointment, the children are not seriously ill, and there is no end in sight, it is time to address the basic needs of the health care providers.

12. *Affirm the resident's strengths:* Sometimes our only responses to residents relate to areas in which they need to improve. We tend to forget that they are already self-critical people and usually well aware of their weaknesses. Do not forget to remind them of their many strengths, eg, curiosity, questioning, healthy skepticism, intellectual honesty about their limitations, initiative, willingness to see difficult families, decisiveness, openness to change, good documentation of information on medical records, good follow-through, and people skills (rapport). Knowing in which areas they are strong gives residents the courage to persevere in the crosscurrents of medicine.

My heartfelt thanks to house staffs of 23 years who have taught me and continue to teach me to be an effective teacher. My special thanks goes to the dedicated members of our section of general pediatrics for reviewing these comments.



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Indications and Usage: For relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold.

Contraindications: Hypersensitivity to any of the ingredients. Do not use in the newborn, in premature infants, in nursing mothers, in patients with severe hypertension or severe coronary artery disease, or in those receiving monoamine oxidase (MAO) inhibitors.

Antihistamines should not be used to treat lower respiratory tract conditions including asthma.

Warnings: Especially in infants and small children, antihistamines in overdosage may cause hallucinations, convulsions, and death.

Antihistamines may diminish mental alertness. In the young child, they may produce excitation.

Precautions: **General:** Because of its antihistamine component, Dimetane DX Cough Syrup should be used with caution in patients with a history of bronchial asthma, narrow angle glaucoma, gastrointestinal obstruction, or urinary bladder neck obstruction. Because of its sympathomimetic component, Dimetane DX Cough Syrup should be used with caution in patients with diabetes, hypertension, heart disease, or thyroid disease.

Information for Patients: Patients should be warned about engaging in activities requiring mental alertness, such as driving a car or operating dangerous machinery.

Drug Interactions: Antihistamines have additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, anxiolytic agents, etc.). MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines. MAO inhibitors may enhance the effect of pseudoephedrine. Sympathomimetics may reduce the effects of antihypertensive drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies of Dimetane DX Cough Syrup to assess the carcinogenic and mutagenic potential or the effect on fertility have not been performed.

Pregnancy

Teratogenic Effects-Pregnancy Category C

Animal reproduction studies have not been conducted with Dimetane DX Cough Syrup. It is also not known whether Dimetane DX Cough Syrup can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Dimetane DX Cough Syrup should be given to a pregnant woman only if clearly needed.

Reproduction studies of brompheniramine maleate (a component of Dimetane DX Cough Syrup) in rats and mice at doses up to 16 times the maximum human dose have revealed no evidence of impaired fertility or harm to the fetus.

Nursing Mothers: Because of the higher risk of intolerance of antihistamines in small infants generally, and in newborns and premature infants in particular, Dimetane DX Cough Syrup is contraindicated in nursing mothers.

Adverse Reactions: The most frequent adverse reactions to Dimetane DX Cough Syrup are: sedation; dryness of mouth, nose and throat; thickening of bronchial secretions; dizziness. Other adverse reactions may include:

Dermatologic: Urticaria, drug rash, photosensitivity, pruritus.

Cardiovascular System: Hypotension, hypertension, cardiac arrhythmias, palpitation.

CNS: Disturbed coordination, tremor, irritability, insomnia, visual disturbances, weakness, nervousness, convulsions, headache, euphoria, and dysphoria.

G.U. System: Urinary frequency, difficult urination.

G.I. System: Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Tightness of chest and wheezing, shortness of breath.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Overdosage: Signs and Symptoms: Central nervous system effects from overdosage of brompheniramine may vary from depression to stimulation, especially in children. Anticholinergic effects may be noted. Toxic doses of pseudoephedrine may result in CNS stimulation, tachycardia, hypertension, and cardiac arrhythmias; signs of CNS depression may occasionally be seen. Dextromethorphan in toxic doses will cause drowsiness, ataxia, nystagmus, opisthotonos, and convulsive seizures.

Toxic Doses: Data suggest that individuals may respond in an unexpected manner to apparently small amounts of a particular drug. A 2 1/2-year-old child survived the ingestion of 21 mg/kg of dextromethorphan exhibiting only ataxia, drowsiness, and fever, but seizures have been reported in 2 children following the ingestion of 13-17 mg/kg. Another 2 1/2-year-old child survived a dose of 300-900 mg of brompheniramine. The toxic dose of pseudoephedrine should be less than that of ephedrine, which is estimated to be 50 mg/kg.

Treatment: Induce emesis if patient is alert and is seen prior to 6 hours following ingestion. Precautions against aspiration must be taken, especially in infants and small children. Gastric lavage may be carried out, although in some instances tracheostomy may be necessary prior to lavage. Naloxone hydrochloride 0.005 mg/kg intravenously may be of value in reversing the CNS depression that may occur from an overdose of dextromethorphan. CNS stimulants may counter CNS depression. Should CNS hyperactivity or convulsive seizures occur, intravenous short-acting barbiturates may be indicated. Hypertensive responses and/or tachycardia should be treated appropriately. Oxygen, intravenous fluids, and other supportive measures should be employed as indicated.

Dosage and Administration: Adults and children 12 years of age and over: 2 teaspoonfuls every 4 hours. Children 6 to under 12 years: 1 teaspoonful every 4 hours. Children 2 to under 6 years: 1/2 teaspoonful every 4 hours. Children 6 months to under 2 years: Dosage to be established by physician.

Do not exceed 6 doses during a 24-hour period. Rev. May 1987.

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Water Intoxication

A Prevalent Problem in the Inner City

The article in this issue of *AJDC* by Keating et al¹ from St Louis, Mo, adds to our warning in 1986 that the incidence of water intoxication in infants has risen during the last 15 years.² Four additional issues not extensively addressed by Keating et al are worth comment.

See also p 985.

First, why has there been a sharp increase in the number of patients with water intoxication? Families living in poverty have diluted formulas and fed water to hungry infants as long as any of us can remember, yet before about 1970 we clinicians working in inner-city hospitals rarely encountered water intoxication as a result. On the contrary, we encountered a high incidence of hyponatremic dehydration between 1945 and 1970.³ I believe the most important factor in bringing about this reversal was the deliberate reduction in the salt (and other "renal solute") content of infant formulas and foods because of concerns about hypertension in later life. Older pediatricians will remember evaporated milk formulas with high solute content. Whether we have achieved a clinically important goal in preventing hypertension remains unknown, but clearly the hyponatremic variety of dehydration is much less common; the percentage of infants hospitalized owing to dehydration decreased from 25% before changes in salt content of formulas to about 2% after these changes were made. This is a welcome outcome because permanent brain damage occurred in 8% to 10% of infants after severe hyponatremic episodes.⁴ On the other hand, water intoxication with con-

vulsion has partially replaced hyponatremia. Patients with cystic fibrosis are especially vulnerable to a low salt intake. Fortunately, permanent neurologic damage is uncommon after water intoxication, so the change in salt content of formulas is ultimately a gain.

A second issue is an understanding of the pathophysiologic aspects of water intoxication, which involves the same physiochemical process, but in reverse, of serious hyponatremic dehydration. For water intoxication to occur, there must be a rapid decline in extracellular solute concentration (osmolality), creating a concentration gradient between extracellular fluid and cell water generally and a gradient between the vascular fluid of the brain and the rest of the brain fluids in particular. The brain is affected differently because, unlike other tissues, the endothelial cells of the cerebral blood vessels are joined by tight junctions (the so-called blood-brain barrier). This means that when an osmolal gradient is produced, relief of the gradient in the brain cannot be quickly achieved by rapid diffusion of sodium and chloride ions from the extracellular fluid of the brain, but must be equilibrated by movement of water molecules into both the extracellular fluid and cells of the brain. Consequently, the brain picks up disproportionately more water than other organs; such swelling causes the convulsion, but only if the dilution occurs over a few hours. If the change is gradual (a few milliosmoles every 12 hours or so), enough sodium chloride diffusion occurs, keeping the respective volumes constant, preventing a convulsion. This rate of change is a key element in the clinical picture of convulsion in hy-

ponatremic states, and it is more important than the degree of hyponatremia. There are other aspects to the adaptation to an osmolal gradient, but none so relevant to the clinical picture.

A third point concerns which patients present with water intoxication. The St Louis group has identified families in which formula dilution or water substitution for formula was most important. In Brooklyn, we have also encountered patients from such families, but formula dilution and water substitution most commonly occurs in patients with mild diarrhea. Often, a physician (sometimes the mother herself, remembering a previous episode of diarrhea) prescribes dilute beverages to replace formula already low in solute. Thus, there is an iatrogenic component to the increased incidence of water intoxication. The lesson is that use of fluids to prevent or correct dehydration should be based on physiologic principles and prescribed with considerable care. The common suggestion of "drink juices, soda, water, and/or an athletic replacement solution" does not suffice.

Finally, how should the patient with water intoxication be treated? The convulsions are usually fairly brief and should be cared for as any others. The hyponatremia can be corrected in many ways. The St Louis group recommends hypertonic saline (0.5 mol/L or 3%) corrected to about 125 mmol/L. While this is a safe procedure if done correctly, it can be very dangerous if an error is made. Having hypertonic solution in the same cabinet with others may also lead to erroneous administration of the solution to a different patient. Patients with water intoxication who

EDITORIAL

do not have renal damage (those discussed in the article by Keating et al do not) will also recover by simple expenditure of insensible water while being given higher than usual amounts of sodium (100 to 150 mmol/L) in fluids. Some may be dehydrated despite water intoxication and need deficit replacement as well as intake of maintenance fluid. I recommend not using hypertonic solutions for this purpose except when

an expert is available to direct the therapy. Our patients with water intoxication (about 10 to 12 per year) thus treated have all recovered well.

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CORRECTION

Incorrect Unit of Measure

In the article entitled "Effect of Necrotizing Enterocolitis on Urinary Epidermal Growth Factor Levels" in the July 1991 issue of *AJDC* (1991;145:804-807), there were some errors in the units of measure used to report EGF and creatinine values. The unit of measure for human EGF values cited five lines from the end of the text under the subhead "EGF Assay and Creatinine Measurements" on page 805 should have read micromoles per liter, and three lines below, the unit of measure for EGF/creatinine values should have read micromoles per micromole. Also, in the last paragraph in the left column of the next page, four lines from the bottom, the values in parentheses should have read $\mu\text{mol}/\mu\text{mol}$, not $\mu\text{mol}/\text{mmol}$.

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INDICATIONS AND USAGE

SURVANTA is indicated for prevention and treatment ("rescue") of Respiratory Distress Syndrome (RDS) (hyaline membrane disease) in premature infants. SURVANTA significantly reduces the incidence of RDS, mortality due to RDS and air leak complications.

Prevention

In premature infants less than 1250 g birth weight or with evidence of surfactant deficiency, give SURVANTA as soon as possible, preferably within 15 minutes of birth.

Rescue

To treat infants with RDS confirmed by x-ray and requiring mechanical ventilation, give SURVANTA as soon as possible, preferably by 8 hours of age.

CONTRAINDICATIONS

None known.

WARNINGS

SURVANTA is intended for intratracheal use only. SURVANTA CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, its use should be restricted to a highly supervised clinical setting with immediate availability of clinicians experienced with intubation, ventilator management, and general care of premature infants. Infants receiving SURVANTA should be frequently monitored with arterial or transcutaneous measurement of systemic oxygen and carbon dioxide.

DURING THE DOSING PROCEDURE, TRANSIENT EPISODES OF BRADYCARDIA AND DECREASED OXYGEN SATURATION HAVE BEEN REPORTED. If these occur, stop the dosing procedure and initiate appropriate measures to alleviate the condition. After stabilization, resume the dosing procedure.

PRECAUTIONS

General

Rales and moist breath sounds can occur transiently after administration. Endotracheal suctioning or other remedial action is not necessary unless clear-cut signs of airway obstruction are present.

Increased probability of post-treatment nosocomial sepsis in SURVANTA-treated infants was observed in the controlled clinical trials (Table 3). The increased risk for sepsis among SURVANTA-treated infants was not associated with increased mortality among these infants. The causative organisms were similar in treated and control infants. There was no significant difference between groups in the rate of post-treatment infections other than sepsis.

Use of SURVANTA in infants less than 600 g birth weight or greater than 1750 g birth weight has not been evaluated in controlled trials. There is no controlled experience with use of SURVANTA in conjunction with experimental therapies for RDS (eg, high-frequency ventilation or extracorporeal membrane oxygenation).

No information is available on the effects of doses other than 100 mg phospholipids/kg, more than four doses, dosing more frequently than every 6 hours, or administration after 48 hours of age.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction studies in animals have not been completed. Mutagenicity studies were negative. Carcinogenicity studies have not been performed with SURVANTA.

ADVERSE REACTIONS

The most commonly reported adverse experiences were associated with the dosing procedure. In the multiple-dose controlled clinical trials, transient bradycardia occurred with 11.9% of doses. Oxygen desaturation occurred with 9.8% of doses.

Other reactions during the dosing procedure occurred with fewer than 1% of doses and included endotracheal tube reflux, pallor, vasoconstriction, hypotension, endotracheal tube blockage, hypertension, hypocarbia, hypercarbia, and apnea. No deaths occurred during the dosing procedure, and all reactions resolved with symptomatic treatment.

The occurrence of concurrent illnesses common in premature infants was evaluated in the controlled trials. The rates in all controlled studies are in Table 3.

TABLE 3

Concurrent Event	All Controlled Studies		
	SURVANTA (%)	Control (%)	P-Value ^a
Patent ductus arteriosus	46.9	47.1	0.814
Intracranial hemorrhage	48.1	45.2	0.241
Severe intracranial hemorrhage	24.1	23.3	0.693
Pulmonary air leaks	10.9	24.7	<0.001
Pulmonary interstitial emphysema	20.2	38.4	<0.001
Necrotizing enterocolitis	6.1	5.3	0.427
Apnea	65.4	59.6	0.283
Severe apnea	46.1	42.5	0.114
Post-treatment sepsis	20.7	16.1	0.019
Post-treatment infection	10.2	9.1	0.345
Pulmonary hemorrhage	7.2	5.3	0.166

^aP-value comparing groups in controlled studies

When all controlled studies were pooled, there was no difference in intracranial hemorrhage. However, in one of the single-dose rescue studies and one of the multiple-dose prevention studies, the rate of intracranial hemorrhage was significantly higher in SURVANTA patients than control patients (63.3% v 30.8%, $P=0.001$; and 48.8% v 34.2%, $P=0.047$, respectively). The rate in a Treatment IND involving approximately 4400 infants was lower than in the controlled trials.

In the controlled clinical trials, there was no effect of SURVANTA on results of common laboratory tests: white blood cell count and serum sodium, potassium, bilirubin, creatinine.

More than 3700 pretreatment and post-treatment serum samples were tested by Western Blot immunoassay for antibodies to surfactant-associated proteins SP-B and SP-C. No IgG or IgM antibodies were detected.

Several other complications are known to occur in premature infants. The following conditions were reported in the controlled clinical studies. The rates of the complications were not different in treated and control infants, and none of the complications were attributed to SURVANTA.

Respiratory: lung consolidation, blood from the endotracheal tube, deterioration after weaning, respiratory decompensation, subglottic stenosis, paralyzed diaphragm, respiratory failure.

Cardiovascular: hypotension, hypertension, tachycardia, ventricular tachycardia, aortic thrombosis, cardiac failure, cardiorespiratory arrest, increased apical pulse, persistent fetal circulation, air embolism, total anomalous pulmonary venous return.

Gastrointestinal: abdominal distention, hemorrhage, intestinal perforations, volvulus, bowel infarct, feeding intolerance, hepatic failure, stress ulcer.

Renal: renal failure, hematuria.

Hematologic: coagulopathy, thrombocytopenia, disseminated intravascular coagulation.

Central Nervous System: seizures.

Endocrine/Metabolic: adrenal hemorrhage, inappropriate ADH secretion, hyperphosphatemia.

Musculoskeletal: inguinal hernia.

Systemic: fever, deterioration.

Follow-Up Evaluations

To date, no long-term complications or sequelae of SURVANTA therapy have been found.

Single-Dose Studies

Six-month adjusted-age follow-up evaluations of 232 infants (115 treated) demonstrated no clinically important differences between treatment groups in pulmonary and neurologic sequelae, incidence or severity of retinopathy of prematurity, rehospitalizations, growth, or allergic manifestations.

Multiple-Dose Studies

Six-month adjusted age follow-up evaluations have not been completed. Preliminarily, in 605 (333 treated) of 916 surviving infants, there are trends for decreased cerebral palsy and need for supplemental oxygen in SURVANTA infants. Wheezing at the time of examination tended to be more frequent among SURVANTA infants, although there was no difference in bronchodilator therapy.

Twelve-month follow-up data from the multiple-dose studies have been completed in 328 (171 treated) of 909 surviving infants. To date no significant differences between treatments have been found, although there is a trend toward less wheezing in SURVANTA infants in contrast to the six month results.

OVERDOSAGE

Overdosage with SURVANTA has not been reported. Based on animal data, overdosage might result in acute airway obstruction. Treatment should be symptomatic and supportive.

Rales and moist breath sounds can transiently occur after SURVANTA is given, and do not indicate overdosage. Endotracheal suctioning or other remedial action is not required unless clear-cut signs of airway obstruction are present.

HOW SUPPLIED

SURVANTA (beractant) Intratracheal Suspension is supplied in single-use glass vials containing 8 mL of SURVANTA (NDC 0074-1040-08). Each milliliter contains 25 mg of phospholipids (200 mg phospholipids/8 mL) suspended in 0.9% sodium chloride solution. The color is off-white to light brown.

Store unopened vials at refrigeration temperature (2-8°C). Protect from light. Store vials in carton until ready for use. Vials are for single use only. Upon opening, discard unused drug.

June, 1991

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Oral Water Intoxication in Infants

An American Epidemic

James P. Keating, MD, MSci(Epidem); Gregory J. Schears, MD; Philip R. Dodge, MD

● Between 1975 and 1990, a total of 34 patients with water intoxication were treated at St Louis (Mo) Children's Hospital, 24 of these in the last 3 years, indicating a marked increase in incidence of this previously rare condition. Thirty-one were infants living in poverty who ingested excessive amounts of water offered at home by their caretakers. Exhaustion of the supply of infant formula was the most common reason given for this substitution. Infants were treated by a single infusion of hypertonic saline or a slow infusion of isotonic saline. Central pontine myelinolysis was not observed as a complication of hypertonic saline therapy. Modification of the Special Supplemental Food Program for Women, Infants, and Children to provide sufficient formula for the growing infant and better education of mothers as to the hazards of excessive water ingestion might reduce the incidence of this preventable and life-threatening condition.

(AJDC. 1991;145:985-990)

In 1922, Larson et al¹ described the acute neurologic disturbance that results from rapid, excessive water intake. Water intoxication has been considered a rare clinical event that follows excessive parenteral or enteral water administration by medical personnel,² malicious forcing of water on a child,³ repeated immersion (infant swimming lessons),⁴ or voluntary ingestion of iced water

infants suffering from water intoxication by the oral route in institutions in five US cities appeared in the medical literature.¹⁰⁻¹⁴ In 1987, Medani¹⁵ described 19 such infants at a single Baltimore (Md) hospital. The possibility that an epidemic is occurring is suggested by these reports and our own experience in the years 1975 through 1990. The details of the clinical syndrome are provided to guide clinicians in the recognition and treatment of the illness. Preventive interventions applicable to the population at risk are discussed.

PATIENTS AND METHODS

St Louis (Mo) Children's Hospital is a 235-bed facility with 50 000 emergency room visits per annum that serves the health needs of a large geographic region. Approximately 60% of patients have private insurance, and 40% are enrolled in Medicaid. There was a modest increase in the number of urban poor cared for when two small pediatric services in municipal hospitals closed 5 to 10 years ago. A second children's hospital (Cardinal Glennon Memorial Children's Hospital) also serves the region's pediatric needs, but no fluctuation in the acute care activities of either children's hospital occurred during the study period of a magnitude that would explain the first appearance and recent increase in the number of infants with oral water intoxication described in this report.

The records of all patients diagnosed as having water intoxication (*International Classification of Diseases, Ninth Edition*, 276.6) were obtained from the Medical Records Department and the Pediatric Gastroenterology Registry at St Louis Children's Hospital for the period from January 1975 through July 1990. All records that contained a description of an acute neurologic syndrome occurring in association with hyponatremia were selected for detailed review and analysis. Information was abstracted from notes of physicians, social workers, emergency medical technologists, and nurses. Follow-up information was sought by telephone interview with each child's current physician or parent if adequate information was not present in the child's chart.

The 34 patients identified by this process were divided into group 1 (infants) (n=31) and group 2 (children) (n=3) for further analysis and to facilitate discussion. The infants were further subdivided by the treatment given (hypertonic saline [group 1a] or a slow infusion [1.0 L/m² per day] of isotonic fluid [group 1b]). A patient's treatment was chosen by the clinicians at the time rather than by randomized assignment as would be done in a prospective study of the efficacy of the therapies. Infants in group 1b were more likely to have been recognized to have water intoxication late in their course; a brisk water diuresis had already occurred. Infants in group 1a received a single infusion of 3% saline given during 30 to 90 minutes. The dose was calculated

See also p 981.

to control toothache⁵ or occurs during marathon runs,⁶ after drug testing,⁷ or as a manifestation of psychosis.⁸ In 1967, Dugan and Holliday⁹ provided the first description of infants who developed water intoxication after the voluntary ingestion of dilute formula. During the following decade and a half, 21 additional examples of healthy in-

Accepted for publication April 18, 1991.

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Table 1.—Infants and Children With Water Intoxication (n = 34)*

Patient/Age, mo		Treatment	Serum Sodium			Temperature, °C†	Respiratory Failure
			Admission, mmol/L	Rate of Increase, mmol·L ⁻¹ ·h ⁻¹	Time Until Normal, h		
Group 1a (n = 17)							
1/3		3%	116	10.0	2	36.0	—
2/9		3%	114	2.5	3	35.4	—
3/6		3%	114	2.0	8	36.7	+
4/1		3%	116	1.7	14	35.0	—
5/3		3%	114	3.0	6	35.0	+
6/4		3%	116	2.5	12	36.5	—
7/6		3%	115	1.7	14	35.0	+
8/4		3%	119	1.8	10	35.0	+
9/4		3%	112	1.7	13	34.0	+
10/3		3%	112	1.7	15	35.2	+
11/4		3%	115	2.8	15	35.2	—
12/3		3%	112	2.2	8	35.0	—
13/4		3%	118	3.6	5	36.4	—
14/4		3%	116	4.4	5	35.4	+
15/4		3%	117	4.4	5	34.2	+
16/4		3%	114	2.7	8	36.7	+
17/10		3%	115	3.3	6	34.0	—
Mean ± SD (range)	4.5 ± 2.2 (1-10)	. . .	115.0 ± 2.0 (112-119)	3.05 ± 2.0 (1.7-10.0)	9.06 ± 4.1 (2-15)	35.3 ± 0.9	9 (53%)
Group 1b (n = 14)							
18/4		NS	118	3.0	5	34.0	+
19/4		0.25 NS	117	2.0	10	35.4	—
20/10		RL	119	1.8	10	36.0	—
21/3		RL	112	1.2	16	34.0	+
22/2		RL	122	2.0	2	36.7	—
23/4		NS	116	3.0	15	36.0	—
24/4		NS	125	1.5	10	36.4	—
25/3		NS	119	1.4	11	35.5	—
26/2		RL	117	2.0	12	36.5	—
27/5		NS	119	1.2	10	35.4	+
28/4		PO	123	3.0	4	36.4	+
29/5		RL	116	1.5	12	37.0	+
30/2		PO	127	1.0	8	36.0	—
31/2		NS	111	1.8	12	35.5	+
Mean ± SD (range)	3.86 ± 2.07 (2-10)	. . .	118.6 ± 4.5 (111-127)	1.89 ± 0.68 (1.0-3.0)	9.79 ± 3.95 (2-16)	35.8 ± 0.9	6 (43%)
Group 2 (n = 3)							
32/8 y		0.5 NS	120	3.0	5	36.2	—
33/3 y		5%	114	2.6	8	34.7	+
34/2 y		3%	112	7.0	30	<34.0	+

*Group 1a consisted of infants intoxicated by the oral route, treated by infusion of 3% saline. Group 1b consisted of infants intoxicated by the oral route, treated with normal saline (NS), Ringer's lactate (RL), or infant formula (PO). Group 2 consisted of children intoxicated by the parenteral or oral route. The difference (1a vs 1b) in initial serum sodium level (15.0 vs 118.6 mmol/L) was statistically significant ($P < .05$). The differences (1a vs 1b) in age, sex, race, rate of serum sodium level increase, time until sodium level was normal, temperature, and proportion of patients with respiratory failure failed to reach statistical significance.

†Temperatures are given as rectal. In seven infants, rectal temperatures were not measured; the number given is their axillary temperature transformed to rectal. In the three infants with temperatures of 34°C, that was the lowest reading possible on the thermometer; they may have been colder.

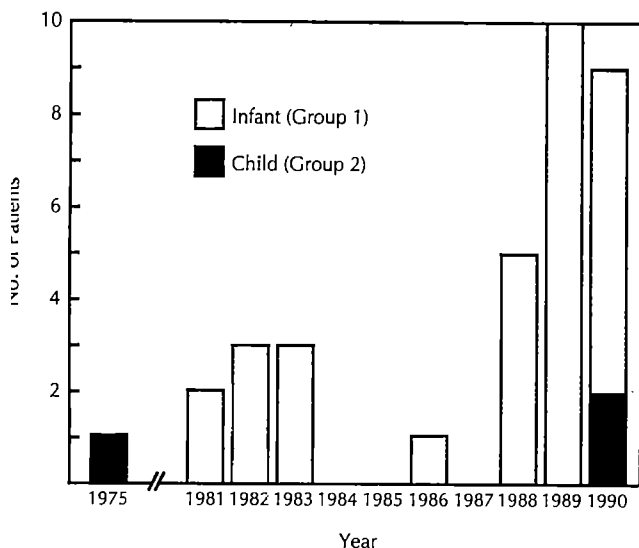


Fig 1.—Frequency distribution by calendar year of all patients diagnosed as having water intoxication between January 1975 and December 1990.

is follows: (body weight in kilograms)(125 mEq/L – initial serum sodium level)(0.6), or about 10 mL of 3% saline per kilogram of body weight.

We obtained records of ambient temperature in St Louis during the years 1988, 1989, and 1990 from the National Oceanic and Atmospheric Administration, US Department of Commerce (Asheville, NC) and compared these with the average temperatures in this area during the last three decades.

The local offices of the Supplemental Food Program for Women, Infants, and Children (WIC) of the State of Missouri/US Department of Agriculture were visited to gather data concerning the availability of food supplements and nutritional advice provided to families in our area during the period of the study. The instructions provided to new mothers by physicians and nurses at St Louis Regional, St Louis Jewish, and Barnes Hospitals (hospitals where most of the infants had been born) were reviewed. Particular attention was paid to changes in allotments of formula and to any advice that might have fostered the substitution of water for formula.

Availability of a clinical microchemistry laboratory and the practice of measuring serum electrolytes in the first sample taken from a convulsing child had not changed during the period of the study.

Descriptive and comparative statistics were calculated by conventional methods, and comparison of means was carried out by test. Comparison of ratios of discrete variables was carried out with the χ^2 test. All tests were two tailed. $P < .05$ was considered statistically significant.

RESULTS

Thirty-four patients were treated for water intoxication, the first infant in 1982 and 24 during the last 3 years (1988 through 1990) (Fig 1). Selected data from each patient are seen in Table 1.

Group 1

The mean \pm SD age of the 31 infants was 4.2 ± 2.1 months; 17 were male. The illness started suddenly with convulsions or apnea. Seizures occurred in all infants and usually (28 of 31 cases) consisted of generalized tonic-clonic activity. Opisthotonic posturing was common (10 of 31 cases). Seizures persisted from 15 minutes to 6 hours, often intermixed with periods of reduced responsiveness. The possibility of continuing, clinically inapparent seizures, the postictal state, and the depressant

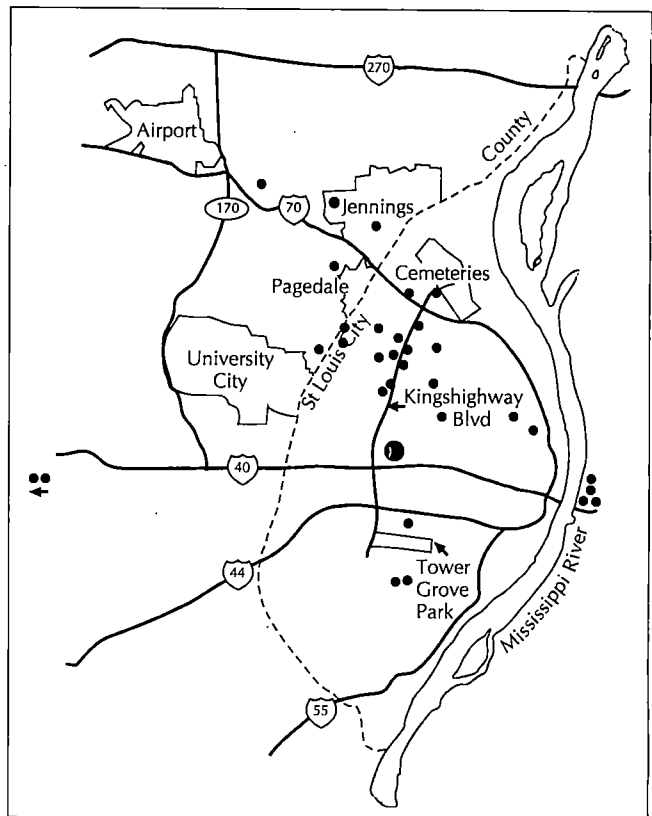


Fig 2.—Map of the St Louis (Mo) metropolitan area. St Louis Children's Hospital (star) is within the city limits. The dots to the extreme right represent infants from East St Louis, Ill. The two dots to the extreme left are two white infants, one from a small city 112 km from St Louis, the other from a suburb 24 km from the hospital. Kingshighway Boulevard is the main north-south traffic artery through a densely populated, poor, residential area.

effect of anticonvulsant medications made determination of causality of the depressed level of consciousness difficult. In several infants, physicians noted rapid improvement in neurologic signs as hypertonic saline was administered. Bulging of the fontanelle and radiologic evidence of increased intracranial pressure were notably absent.

Respiratory failure, neither preceded nor obviously caused by seizure, occurred in six patients, either at home (five patients) or in the radiology suite (one patient). Others stopped breathing in the emergency room (nine patients). The overall rate of respiratory failure was 15 of 31 (48%). Except in one infant who developed noncardiologic pulmonary edema, mechanical ventilation was withdrawn within 24 hours of admission.

Mean \pm SD laboratory values (Table 1) included the following: urine specific gravity (31 of 31 patients), 1.004 ± 0.001 ; serum urea nitrogen (31 of 31 patients), 1.4 ± 0.4 mmol/L; serum calcium (31 of 31 patients), 2.40 ± 0.07 mmol/L; serum magnesium (29 of 31 patients), 0.88 ± 0.03 mmol/L; and serum glucose (31 of 31 patients), 5.5 ± 0.67 mmol/L. Cerebrospinal fluid (29 of 31 patients) was sterile and contained a nucleated cell count of less than 8×10^6 /L. The serum cortisol level (24 patients) was within the normal reference range, as was the blood ammonia level (25 patients). A urine toxic screen (26 patients) failed to reveal substances capable of causing seizures, respiratory failure, or hyponatremia. The mean platelet count (31 of 31 patients) was 615×10^9 /L (range, 250 to 1300×10^9 /L). Imaging studies of the brain (computed to-

mography, ultrasound, skull roentgenography) were carried out in 19 of the 31 infants, and no evidence of trauma, structural abnormalities, or gross cerebral edema was found. Results of neurologic and developmental examinations carried out before discharge were within the expected range for the infants' ages. With the exception of one infant who was jaundiced on admission and was found to have extrahepatic biliary atresia, and one who was found at a later admission to have a nonaccidental fracture of the humerus, there was no evidence of another illness. The subsequent developmental progress of all but one infant has been within the acceptable range.

The excessive water was usually ingested as tap water from an 8-oz baby bottle. The rate of water intake was about 7.5 L/m² per day, and the period during which it was taken was as brief as 1½ hours, but in most cases it was 2 to 8 hours. In several infants, the caregiver mixed formula with three to four times the usual amount of water rather than offering water alone. The caregivers' explanations for the water substitution were as follows: ran out of formula (16), gave water for diarrhea (four), gave water because of irritability or fussiness (three), infant was fed by more than one person, with poor communication about contents of previous bottles (one), infant "always" drinks a lot (two), infant "very thirsty" (two), friend said water was good for infection (one), infant was offered water because it was a very hot day (one), and no explanation (one).

Twenty-eight of the 31 infants lived within 8 km of our hospital (Fig 2), most in residential areas known to have high lead exposure risk, high crime rates, and poverty. Twenty-seven infants were black. Twenty-seven were enrolled in WIC, Aid to Families With Dependent Children, and the food stamp program. Only one mother was married; three were addicted to crack cocaine and alcohol. Most of the mothers were in their 20s and 30s and had older children (one had seven).

Since the WIC program began in 1976, the maximum provision of infant formula has been one can of formula per day per infant (403 fl oz of concentrated liquid formula per month) through the first 12 months of life. In some areas this is provided as an equivalent amount of powdered or ready-to-feed formula. This allotment provides 2293 kJ, or a little more than three 8-oz bottles per infant per day. Based on the average body weight of 4-month-old infants, this provides 378 kcal/kg per day, which is approximately the 50th percentile of observed intake of healthy 4-month-old infants. A small amount of juice and cereal is provided after age 4 months. The mothers of many of our patients found themselves using more than one can per day and exhausted the WIC-supplied formula before the end of the month. The WIC nutritionists, and our hospital social workers, reported a disappearance of alternate (non-WIC) sources of free infant formula and a sharp increase in the cost of formula in retail outlets during the last decade. Sources of additional formula, which in the past were manufacturers' representatives, food pantries, and local churches, appear to have been eliminated. The WIC workers emphasize the word *supplemental* in the program title, but they recognize that many mothers presume that WIC provides everything the infant needs and are reluctant or unable to use their food stamps or cash to buy infant formula. Advice concerning water feeding has been the same since the program began in 1976: "After the infant has taken the breast or formula,

you may offer a little water if he/she seems to want it," offered to the mother at the time of enrollment in an individual counseling session by a nutritionist. We uncovered no major change in advice during the study period by WIC workers or by personnel of the institutions where the infants were born.

Of the 31 infants, 22 developed symptoms during the summer months (May through October vs November through April) ($\chi^2=9.2$, $P<.05$). Average temperatures during May through October of 1988, 1989, and 1990 did not exceed the average values for those months during the previous decade; 1989 was cooler and 1990 was hotter than the average.

Group 2

Water intoxication in older children remains a rare event; in contrast to group 1, the incidence did not appear to have changed.

Patient 32, an 8-year-old girl, had suffered from physical abuse as an infant and had openly stated her intention to stab to death a foster parent. Her foster parents, after much counseling, chose water drinking as a method of punishment. When forced to stand in the kitchen and drink 12 glasses of water, the patient lost consciousness. Her recovery was complete.

Patient 33, a 3-year-old girl, was admitted to an outlying hospital with severe dehydration (serum urea nitrogen level, 23.6 mmol/L) due to gastroenteritis. Fluid resuscitation (40 mL/kg) was carried out with the use of 5% glucose in water instead of the intended 5% glucose in saline. As the 4-hour infusion ended, the patient lost consciousness, serum sodium level decreased from 133 to 114 mmol/L, and apnea and coma ensued; hypertonic saline and nonspecific measures were of no avail, and the patient died. Autopsy showed only brain swelling.

Patient 34, who was 2 years old, became comatose 4 hours after elective hip surgery. Serum sodium level had decreased to 112 mmol/L while dilute intravenous fluids were infused. Again, therapy had no apparent effect, and autopsy showed brain swelling. The vulnerability of postoperative patients to water intoxication has been emphasized,^{2,16} and the devastating course in such patients has recently been described.¹⁷

COMMENT

Oral water intoxication is a recognizable clinical syndrome. The victim is usually 3 to 6 months old, comes from a poor family, and presents to the ambulance service or emergency room with apnea or seizures. Body temperature is low, even in hot weather, and the majority of episodes occur in the summer months. Respiratory failure, if not the presenting complaint, may occur as the seizures are treated. After documentation of hyponatremia and the infusion of hypertonic saline, the neurologic disturbance abates. In some infants, spontaneous water diuresis occurs so rapidly that treatment with hypertonic saline may be unnecessary. Ventilatory support is seldom needed for more than 12 hours, and recovery appears complete within a few days. The infants' salt and water homeostatic mechanisms are intact, and, with appropriate feeding instructions, recurrence can be avoided. There is clearly some risk of death or hypoxic organ damage, although this did not occur in our patients (group 1).

The controversy^{18,19} that surrounds the treatment of chronically hyponatremic adults and the belief that ex-

Table 2.—Oral Water Intoxication in 85 Healthy Infants

Source, y	City	No. of Patients	Age, mo	Comments
Dugan and Holliday, ⁹ 1967	Pittsburgh, Pa	1	3	Errors in mixing; ½ strength formula
Dugan and Holliday, ⁹ 1967	Oakland, Calif	1	5	Ten 8-oz bottles of water over 20 h
Nickman et al, ¹⁰ 1968	Philadelphia, Pa	2	4, 14	Fed water
Crumpacker and Kriel, ¹¹ 1973	Minneapolis, Minn	5	5.8 ± 4.1	Short of money; gave 12 8-oz bottles of tap water in 1 d; "Hunger is probably the main force that would compel a baby to accept a solute-poor diet . . ."
Schulman, ¹² 1980	Albany, NY	2	5, 6	Ran out of milk; gave 64 oz of tap water
David et al, ¹³ 1981	Pittsburgh	8	3.4 ± 1.0	Authors focused on antidiuretic hormone secretion
Partridge et al, ¹⁴ 1981	Cincinnati, Ohio	4	4.1 ± 1.5	Two sibling pairs; water given after each feeding for irritability; physical abuse in one family
Lipsitz, ²⁶ 1984	Pueblo	1	2.5	Water and tea substituted due to coryza
O'Connor, ²⁷ 1985	Wilmington, Del	1	2	Water fed because of diarrhea
Corneli et al, ²⁸ 1985	Cincinnati	7	6.7 ± 1.8	All occurred in 6-wk period, summer 1983
Gold and Koenigsberg, ²⁹ 1986	Chicago, Ill	1	4	Tap water given because of summer heat
Borowitz and Rocco, ³⁰ 1986	Nashville, Tenn	2	5, 3	Considered previous salt restriction important
Medani, ¹⁵ 1987	Baltimore, Md	19	5.1 ± 4.3	Water supplements
Schaeffer and Ditchek, ³¹ 1991	Brooklyn, NY	3	4, 6, 10	...
Present report	St Louis, Mo	31	4.2 ± 2.1	...

cessively rapid administration of hypertonic saline may cause central pontine myelinolysis should not unduly influence physicians caring for acutely hyponatremic children. The rate of increase in serum osmolality/sodium recommended in the former group of patients (less than 0.5 mmol/h)¹⁸ is inappropriate in acutely hyponatremic patients, such as those described in this report. For symptomatic patients with acute hyponatremia, the rate of increase should be at least 1 mmol/L per hour¹⁹; the rate of 2 to 3 mmol/L per hour that occurred in our patients (Table 1) was associated with an excellent overall outcome. The rate of increase in serum osmolality in the infants who had spontaneous diuresis (group 1b) was threefold faster than the maximal recommended rate of correction in the chronically hyponatremic adult. The safety and efficacy of prompt infusion of hypertonic saline in the amounts recommended by current pediatric authorities²⁰⁻²² is supported by our experience. We recognize the limits of our retrospective study and cannot reject the possibility that isotonic fluids at a restricted infusion rate may be effective therapy for many infants, although we think that a more rapid reversal of the movement of water into the brain may be lifesaving in some.

Incidence figures for water intoxication are not available. Since 1935, when the first report²³ of fatal water intoxication appeared, until 1958, only seven patients, of all ages, were noted in the literature.²³⁻²⁵ In 1959, Crawford and Dodge² described five children, three intoxicated by parenteral fluids, one by gastrostomy, and one by enemas. After the first report of infants who took excessive water by mouth appeared in 1967,⁹ only seven similar infants were observed in the next decade,^{10,11} but, during the last 5 years, 33 examples^{15,26-30} have appeared. Table 2 summarizes 85 reported cases of water intoxication.^{9-15,26-31} An article in the lay press in 1981 mentioned 17 Milwaukee (Wis) infants who were not described in the medical litera-

ture.³² We found only three reports³³⁻³⁵ of infants with oral water intoxication from other countries. The ages of those infants were more evenly distributed through the 1st year of life than in the American patients; withdrawal of formula or breast before excessive water ingestion was a consistent theme in these reports.

The reason for the striking increase in the occurrence of oral water intoxication is not clear. Although other investigators have suggested that abusive caretakers,¹⁴ excessive secretion of antidiuretic hormone,¹³ or previous salt restriction may have played a role in their patients, we share Crumpacker and Kriel's view¹¹ that hunger overwhelms the infants' innate protective mechanisms and is the most important cause of infantile water intoxication. Three facts strongly suggest that unavailability of formula plays a major causative role: (1) the current volume of formula provided by WIC meets the needs of most 3-month-olds and fails to satisfy many 4- and 5-month-old healthy infants; (2) in our study, and in most US reports (Table 2), the ages of the infants are 4 to 6 months; and (3) the majority of mothers said that exhaustion of their supply of formula was the reason they were feeding water. Even when another explanation for water feeding was recorded in the patient's chart, specific history concerning the family's formula supply may not have been sought or offered. We also speculate that the summer clustering may be due to the added burden placed on the families' limited resources by the interruption of the school lunch program for the older siblings and other children in the home.

We are convinced that oral water intoxication is a new, probably underreported, entity. A prospective, national, epidemiologic study is needed to ascertain the incidence of and causative factors responsible for this illness. Immediate consideration should be given to increasing the availability of formula to infants living in poverty. Increased education concerning the dangers of excessive water intake in infants who are denied formula or breast-

feeding is also needed,³⁶ both for medical personnel and for infant caregivers.

Our gratitude to the pediatric interns, residents, nurses, and staff physicians in the emergency room, pediatric intensive care unit, and floors of St Louis Children's Hospital, and to the medical record room staff, the social workers, WIC nutritionists, and the child neurology staff, all of whom saw the infants' needs and met them, documenting what they saw and did. The suggestion concerning the cause of summer clustering came from Rebecca Graves, the able director of the St Louis Children's Hospital social work department. Thanks to Aileen Derhake, whose transformation of handwritten gibberish into clean prose raises the skill of typing to a profession.

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ARCHIVES OF GENERAL PSYCHIATRY

Comorbidity of Psychiatric Diagnoses in Anorexia Nervosa

Katherine A. Halmi, MD; Elke Echert, MD; Peggy Marchi, PhD; Vincent Sampugnaro, MA; Robin Apple, MA; Jacob Cohen, PhD
(*Arch Gen Psychiatry.* 1991;48:712-718)

Vasopressin Levels in Infants During the Course of Aseptic and Bacterial Meningitis

Guadalupe Padilla, MD; M. Gore Ervin, PhD; Michael G. Ross, MD; Rosemary D. Leake, MD

● We measured urine vasopressin (VP) once daily on days 1 through 3 in 18 patients hospitalized with meningitis. Urine VP values were 215 ± 100 , 116 ± 44 , and 69 ± 23 pg/mL on days 1 through 3, respectively, for children with bacterial meningitis and 34 ± 14 , 20 ± 4 , and 15 ± 4 pg/mL for those with aseptic meningitis. Urinary VP levels of infants with bacterial meningitis were significantly greater than those of healthy ambulatory subjects ($n=18$) on all three study days; VP values of infants with bacterial meningitis were also greater than those of infants with aseptic meningitis on study days 2 and 3. The VP levels for the subjects with aseptic meningitis were significantly greater than those of the controls on day 1 only. None of the infants exhibited the clinical syndrome of inappropriate antidiuretic hormone secretion.

(AJDC. 1991;145:991-993)

The occurrence of the clinical syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in meningitis implies that circulating vasopressin (VP), or antidiuretic hormone, levels are elevated in this condition. Limited data are available, however, reporting only single values of serum, urine, or spinal fluid VP levels in pediatric patients with meningitis.¹⁻⁷ These reports suggest that SIADH is a risk for children with meningitis but do not document the time course of increased VP secretion during the illness. In this study, we measured urinary VP levels by radioimmunoassay,⁸ as well as serum and urinary sodium levels and osmolality, in infants with bacterial meningitis (BM) and aseptic meningitis (AM). These data quantify VP during the initial 3 days of illness, relate values to responses in serum and urinary sodium levels and osmolality, and allow a comparison of VP levels in BM and AM over time.

PATIENTS AND METHODS

Consent for the study before its initiation was obtained from the Human Subjects' Protection Committee. During the period

from March 1985 to April 1988, we studied 18 infants during the first 3 days of their hospitalizations for meningitis at the Harbor-UCLA Medical Center, Torrance, Calif. Ten patients were diagnosed as having BM, and eight had AM. Patients with hypovolemia, dehydration, or renal, cardiac, pulmonary, or central nervous system diseases other than meningitis were excluded from the study.

The cerebrospinal fluid evaluation consisted of cell count, glucose, protein, and latex agglutination determinations and bacterial/viral cultures. The patients with BM had positive culture and/or latex agglutination results. *Haemophilus influenzae* was cultured in eight infants and meningococcus in two patients. Those diagnosed as having AM had negative culture and latex agglutination results but demonstrated cerebrospinal fluid cell numbers and types consistent with AM. Viral cultures yielded echovirus 17, coxsackievirus B₂, or no growth ($n=6$). No infant received antibiotic therapy before lumbar puncture; all received ampicillin, gentamicin, chloramphenicol, and/or cefotaxime throughout the 3 study days.

A single urine sample was collected from a bladder catheter or spontaneous void within the first 24 hours of hospitalization and for 2 days thereafter for urinary osmolality, sodium, and VP determinations. Urinary VP levels were also measured in single, freely voided urine samples from 18 healthy nonhospitalized children of similar age receiving fluid ad libitum. Serum sodium and urea nitrogen levels were measured daily within 8 hours of the urine sample collection in the patients with meningitis. Serum osmolality was measured directly or calculated by means of the following formula: $\text{osmolality} = 2(\text{sodium}) + \text{serum urea nitrogen} / 2.8 + \text{glucose} / 18$.

The infants' charts were reviewed daily for fluid and sodium intake, for evidence of the clinical syndrome of SIADH, and specifically for a history of hypoxia, pneumothorax, seizures, ventilator therapy, use of volume expanders, and drug administration.

Initial fluid management consisted of 0.9% sodium in 5% glucose infused at rates calculated to provide maintenance needs for all infants. As tolerance allowed, enteral feedings were begun at rates calculated to provide fluid maintenance.

Urine VP levels were measured by radioimmunoassay by means of a method previously described in our laboratory.⁸ Urine samples were collected in plain glass tubes containing 1N hydrochloric acid and stored frozen at -20°C until extraction with disposable columns (C18 SepPak, Milford, Mass). Each sample was assayed in duplicate. Standardized samples were assayed to determine the amount of VP recovered per assay; all values were corrected for recovery rate. Intercoefficients and intracoefficients of variation of the VP assay were 3% and 9%, respectively. Urinary sodium was measured by flame photometry (Instrumentation Laboratories, Watertown, Mass). Urine osmolality was determined by freezing-point depression by means of

Accepted for publication April 10, 1991.

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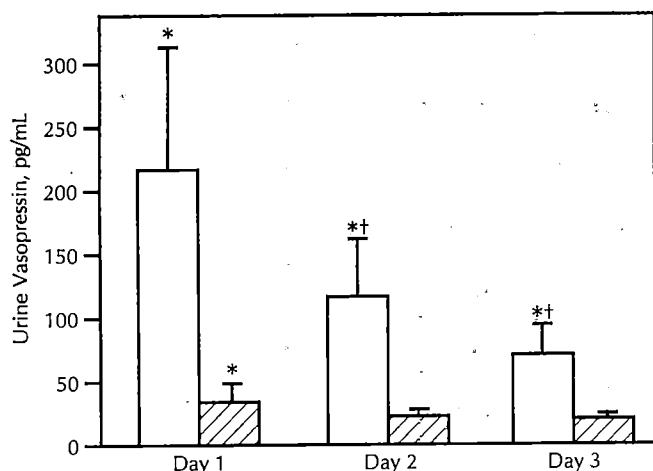


Fig 1.—Mean (\pm SEM) urine vasopressin levels over the 3 study days for infants with bacterial (open bars) and aseptic (crosshatched bars) meningitis ($n=18$). Mean value for a single vasopressin measurement in 18 healthy, age-matched controls was 16.3 ± 2 pg/mL. Asterisk indicates $P < .05$, greater than controls; dagger, $P < .05$, bacterial meningitis greater than (time-matched) aseptic meningitis values.

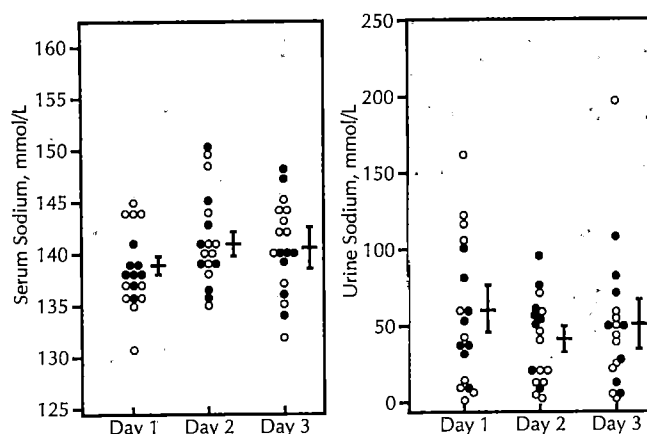


Fig 2.—Serum and urine sodium levels during the 3 study days for patients with bacterial (open circles) and aseptic (closed circles) meningitis. Bars show mean (\pm SEM) for each day.

an osmometer (Digimatic, Advanced Instruments, Needham Heights, Mass). Serum sodium and urea nitrogen concentrations were measured in the hospital laboratory by standard methods.

The VP values for the three study groups were compared by analysis of variance with pairwise comparisons between groups. To achieve a normal distribution with equal variances in each group, log values of the vasopressin levels were used for statistical comparisons. Log VP values were also compared by linked correlation with urinary osmolality (linear regression analysis).

RESULTS

Mean (\pm SEM) ages of the patients with BM and AM were 10.3 ± 2 months and 2.8 ± 1 months, respectively. The mean age of the healthy controls was 7.2 ± 1 months. One patient with BM required placement of a subdural catheter on study day 3. Two patients had single generalized seizures; one required intubation for several hours after the seizure but was not hypoxic. Two patients with BM received phenytoin for seizure activity, and two patients with BM received furosemide; however, all doses were given 8 to 12 hours after urine samples were obtained. One patient received dexamethasone and one

received prednisolone sodium succinate throughout the hospital course.

Urine VP levels in patients with BM and AM are shown in Fig 1. In subjects with BM, mean (\pm SEM) VP values were 215 ± 100 pg/mL on study day 1, 116 ± 44 pg/mL on day 2, and 69 ± 23 pg/mL on day 3. The VP values for the subjects with AM were 34 ± 14 , 20 ± 4 , and 15 ± 4 pg/mL on days 1, 2, and 3, respectively. The urine VP level for the control subjects was 16.3 ± 2 pg/mL. The VP levels of patients with BM were significantly greater ($P < .01$) than those of the control subjects on all 3 study days; the VP values in BM were also greater than those in AM ($P < .05$) on study days 2 and 3. The VP levels of the infants with AM were significantly greater ($P < .05$) than those of the controls on day 1 only.

Maintenance daily fluid requirements were provided for all subjects, and all infants were clinically euvolemic. Mean (\pm SEM) fluid intake in the patients with BM was 88 ± 9 mL/kg per day on day 1, 100 ± 11 mL/kg per day on day 2, and 110 ± 11 mL/kg per day on day 3; thus, there was a gradual increase in intake amounting to 25% by the 3rd day of the study. Fluid intake in the patients with AM was 97 ± 13 , 113 ± 15 , and 109 ± 10 mL/kg per day on days 1, 2, and 3, respectively.

Mean sodium intake was 5.6 ± 1 , 6.6 ± 2 , and 4.6 ± 1.3 mEq/kg per day for patients with BM. Infants with AM received 3.3 ± 1 mEq/kg per day on day 1; oral feedings were resumed on day 2 or 3. Serum and urine sodium levels of patients with BM and AM are shown in Fig 2. Mean serum sodium level was 139 ± 1.5 , 141 ± 1.4 , and 140 ± 1.5 mmol/L for patients with BM on days 1 through 3, respectively, and 138 ± 0.6 , 141 ± 1.9 , and 140 ± 2.4 mmol/L for patients with AM. Only one subject (with BM) exhibited a serum sodium level below 135 mmol/L, and then only on day 1. Mean urine sodium values were 64 ± 18 , 30 ± 7.8 , and 50 ± 7 mmol/L on days 1 through 3, respectively, for patients with BM and 52 ± 11 , 52 ± 10 , and 51 ± 13 mmol/L for patients with AM. Mean serum osmolality was 282 ± 3 , 285 ± 2 , and 284 ± 2 mmol/kg for the patients with BM and 282 ± 2.5 , 288 ± 5.7 , and 287 ± 1 mmol/kg for the patients with AM on days 1 through 3, respectively. Urine osmolality was 578 ± 87 , 664 ± 100 , and 469 ± 46 mmol/kg for the patients with BM and 461 ± 66 , 369 ± 33 , and 491 ± 79 mmol/kg for the patients with AM. There was a significant correlation coefficient ($r = .6$) of log VP and urine osmolality but no correlation with serum or urinary sodium level.

COMMENT

The VP levels in this study represent, to our knowledge, the first reported serial values during the course of meningitis and the first comparisons of VP values and fluid intake, serum and urinary sodium levels, and osmolality in this study population.

Urinary VP levels provide a noninvasive, integrated index of VP secretion. Plasma and (extracted) urine VP correlate linearly, whether compared as urinary VP concentration or rate of VP excretion.⁹ The source of urinary VP is glomerular filtration¹⁰; urinary VP levels correlate significantly with creatinine clearance.^{11,12} Urinary VP levels increase with hypoxia, mask ventilation, the occurrence of pneumothorax, intraventricular hemorrhage in the newborn period, and head trauma in pediatric patients.^{13,14}

With the use of urinary VP determination, we con-

firmed that during the 1st day of illness, patients with both BM and AM exhibit markedly elevated VP levels. On subsequent days, VP levels return toward normal, more rapidly for patients with AM than BM.

The stimulus for increased VP secretion in meningitis is unclear. The VP values cannot be explained on the basis of the therapies administered for meningitis, since phenytoin inhibits VP secretion,¹⁵ and dexamethasone has been reported to increase sodium excretion and produce diuresis or to have no effect.¹⁶

Urine osmolality correlated well with log VP levels in our study; with urine VP measured in unextracted urine,⁴ urine osmolalities were not increased despite high VP levels. We previously reported that a urine osmolality greater than 800 mmol/kg was associated with markedly increased urine VP levels (200 to 1650 pg/mL) in pediatric head trauma¹⁴ (mean age, 7.5 ± 1.6 years). In the younger subjects included in this study, a urine osmolality of greater than 600 mmol/kg was associated with urinary VP levels ranging from 98 to 1038 pg/mL, perhaps reflecting the limitation in any additional urinary concentrating ability of our younger subjects.

Despite the elevated VP and urine osmolality levels and the lack of fluid restriction, none of the patients demonstrated the complete clinical SIADH (hyponatremia, increased urinary sodium concentration, diminished serum osmolality, and urine osmolality greater than serum osmolality). The reported incidence of SIADH varies from 4% to 88% and from 9% to 64% for bacterial and viral meningitis, respectively.¹⁻⁷ In most studies, however, VP blood and urine levels were not measured. There are a number of possible explanations for our low incidence of SIADH. Our series may have been too limited, the VP increase insufficient or too short-lived, and/or the fluid administration inadequate to produce SIADH in this group of moderately ill patients with meningitis. It remains unclear whether patients who are older or experience meningitis associated with asphyxia,¹⁷ cerebral edema,¹⁴ or effusion¹⁸ might secrete more VP and/or respond differently. Moreover, the age at study differed significantly for our patients with BM vs AM (10.3 ± 2 vs 2.8 ± 1 months, respectively). This may have affected VP secretion, although previous studies suggest an intact, appropriate response from birth onward.^{11-13,17,19} Developmental changes in renal response to elevated VP levels, however, have not been well studied in infancy. Thus, our series represents a limited examination of the entire question of VP secretion in childhood meningitis, since our study subjects were too few to analyze by organism, adjunctive therapies, or severity of disease, for example. It is clear from our serial measurements that VP secretion continues despite treatment of meningitis, and although several of our subjects appeared well enough to be discharged on day 4 of hospitalization, their VP levels remained elevated and continued to be a potential risk for development of SIADH.

This work was supported in part by grant HD-06355 from the National Institute of Child Health and Human Development, Bethesda,

Md, and by grant RR-00425 (General Clinical Research Center) from the National Institutes of Health, Bethesda.

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Demographic and Risk Factors Associated With Chronic Dieting in Adolescents

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• A comprehensive, school-based survey was administered to 36 320 Minnesota public school students in grades 7 through 12 during the 1987-1988 school year. Self-reported chronic dieting was much higher in girls than in boys (12.1% of all girls vs 2.1% of boys). For girls, the percentage of chronic dieters was significantly less in grades 7 and 8 (7.8%) than in grades 9 and 10 (13.5%) or grades 11 and 12 (14.3%). There were no differences among urban, suburban, or rural youth. Black girls were less likely to diet compared with white girls. Chronic dieters were more likely than other students to report maladaptive weight-loss techniques, such as self-induced vomiting (relative risk, 9.92 for girls and 9.40 for boys), laxative use (relative risk, 7.18 for girls and 11.00 for boys), ipecac use (relative risk, 8.33 for girls and 11.00 for boys), and diuretic use (relative risk, 7.30 for girls and 13.5 for boys). It is suggested that chronic dieting may serve as a screening marker for more severe eating and weight-loss behaviors.

(AJDC. 1991;145:994-998)

During adolescence, both boys and girls become preoccupied with and sensitive about their size and physical appearance. Studies have consistently shown a high prevalence of dissatisfaction with body weight or shape among male and female adolescents.¹⁻⁵ The cultural pressure to be thin, especially for female adolescents, coupled with the societal stigma of obesity, may predispose weight-conscious youth to abnormal eating patterns and eating disorders.^{6,7} Disordered eating behaviors—unhealthy preoccupation with weight and food, crash diets, fasting, binge eating, and purging—appear to be quite common, especially among female adolescents and young adults.¹⁻⁵ The National Adolescent Health Survey (1988) found that 61% of adolescent girls and 28% of adolescent boys had dieted during the previous year. Unhealthy weight control methods were common among the dieters: 51% reported fasting,

16% used diet pills, and 12% reported vomiting to control their weight.⁸ Johnson et al⁹ surveyed 1268 high school girls and found that 36% were currently dieting and 14% were chronically dieting. Killen et al¹⁰ found that 10.6% of female teenagers reported self-induced vomiting for weight control, while 13% reported some form of purging behavior (vomiting and use of laxatives or diuretics). Recent studies indicate that weight concerns and dieting practices are now occurring with greater frequency than was previously reported among older children and very young teenagers.^{11,12} Maloney et al¹¹ found that 45% of 8- to 13-year-old boys and girls wanted to be thinner and that 37% had already tried to lose weight.

Several authors have proposed that dieting is a predisposing factor in the development of bulimic symptoms as well as the more serious eating disorders anorexia nervosa and bulimia nervosa.^{6,7,9,13,14} Little is known, however, about the prevalence of excessive dieting or if it is associated with other unhealthy eating or weight-loss behaviors. Research on prevalence rates of abnormal eating and of attending demographic risk factors is necessary for the nature and extent of these problems to be understood. Although there are a number of descriptive studies of prevalence of dieting and disordered eating patterns among adolescents and young adults, these tend to be based on relatively small and very select samples, often in private schools or on university campuses, and focus primarily on girls. Therefore, little is known about dieting in relation to sociodemographic characteristics.

We present a descriptive study of unhealthy eating and dieting behaviors based on 34 196 Minnesota youth 12 to 18 years of age. Because repeated dieting constitutes a risk factor for eating disorders as well as inappropriate eating behavior among adolescents, we selected chronic dieting as our chief dependent variable. The distinctive feature of our study is that the sample size of youth from throughout the state of Minnesota is large enough to determine, with some confidence, the relationships of chronic dieting to important sociodemographic characteristics, such as school grade, sex, race, socioeconomic status (SES), and geographic location (urban, suburban, and rural). Furthermore, we examined the relationships of chronic dieting to other disordered eating behaviors.

Accepted for publication January 28, 1991.

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Table 1.—Dieting and Weight-Related Questions From the Minnesota Adolescent Health Survey

How often have you gone on a diet during the last year? By "diet," we mean changing the way you eat so you can lose weight.

Never
1-4 times
5-10 times
More than 10 times
Am always dieting

At the present time, do you feel like you are:
Underweight
About the right weight
Overweight

At this time, how satisfied are you with your weight?
Very satisfied
1 2 3 4 5 6 7 Not at all satisfied

At this time, how proud are you of your body?
Very proud
1 2 3 4 5 6 7 Not at all proud

How often do you vomit (throw up) on purpose after eating?
Never
Once a month or less
2-3 times a week
Once a week
2 or more times a week

Do you use any of the following to lose weight?
Laxatives
Ipecac
Diuretics (water pills) not just for your period
None of the above

Have you ever eaten so much food in a short period of time that you felt out-of-control and would be embarrassed if others saw you (binge-eating, gorging, or bulimia)?
Yes No

Are you ever afraid to start eating because you think you won't be able to stop?
Yes No

SUBJECTS AND METHODS

The Minnesota Adolescent Health Survey was administered from September 1987 to May 1988 and involved 36 320 Minnesota public school students in grades 7 through 12 in 86 school districts. Schools were selected to elicit participation from different ethnic and geographic groups after stratifying for size of school districts. This sample, however, cannot be considered statistically representative of all of Minnesota in a technical sense. Nevertheless, to our knowledge, it is the largest study ever undertaken on youth in America. After the exclusion of obvious errors and inconsistent and incomplete data, usable data were obtained for 34 196 subjects.

The Minnesota Adolescent Health Survey questionnaire covered a broad range of subject areas related to adolescent health. Questions included health care utilization, major worries and concerns, sexuality, emotional stress, suicide attempts, and substance use. A series of questions dealt with body image, weight satisfaction, and eating and weight-loss behaviors (Table 1).

Adolescents were considered "chronic dieters" if they reported that they had been on a diet more than 10 times during the past year or were always dieting during the past year. Because the percentage of chronic dieters among boys was so different from that among girls, analyses were performed for boys and girls separately. Other variables of interest included race/ethnicity, geographic location (urban, suburban, rural), and a measure of parental SES, based on educational attainment and work status. A variable concerning body image was derived from satisfaction with current weight and the response to the question "How proud are you of your body?" Those with high levels of dissatisfaction and low body pride were considered to have a poor body image. Self-reported height and

Table 2.—Selected Characteristics of Minnesota Youth in the Adolescent Health Survey

Variable	No. (%)
Sex	
M	16 725 (48.9)
F	17 471 (51.1)
Grade	
7 and 8	10 445 (30.6)
9 and 10	11 613 (34.0)
11 and 12	12 138 (35.4)
Location	
Urban	16 772 (49.0)
Suburban	5660 (16.6)
Rural	11 764 (34.4)
Parental socioeconomic status	
Low	3937 (12.8)
Moderate	16 681 (54.2)
High	10 165 (33.0)
Ethnicity	
W	28 901 (86.4)
B	2603 (7.8)
Hispanic	343 (1.1)
American Indian	551 (1.6)
Asian	1053 (3.1)
Dieted during the last year	
F	10 832 (61.9)*
M	3512 (20.1)*
Chronic dieters	
F	2104 (12.0)*
M	364 (2.1)*

*Percent of sex class who dieted or were chronic dieters.

Table 3.—Percent of Chronic Dieting by Selected Characteristics Among Adolescent Male and Female Subjects*

	Female Subjects		Male Subjects	
	%	95% CI	%	95% CI
Grade				
7 and 8	7.8	(7.1, 8.5)	1.6	(1.3, 2.0)
9 and 10	13.5	(12.6, 14.4)	2.5	(2.1, 2.9)
11 and 12	14.3	(13.4, 15.2)	2.4	(2.0, 2.8)
Location				
Urban	11.1	(10.5, 11.8)	2.2	(1.9, 2.5)
Suburban	13.8	(12.5, 15.1)	1.8	(1.3, 2.3)
Rural	12.5	(11.7, 13.4)	2.3	(1.9, 2.7)
Parental socioeconomic status				
Low	10.2	(9.0, 11.5)	2.0	(1.4, 2.7)
Moderate	12.6	(11.9, 13.3)	2.2	(1.9, 2.5)
High	12.1	(11.2, 13.0)	2.0	(1.6, 2.4)
Race/Ethnicity				
W	12.5	(11.9, 13.0)	2.1	(1.8, 2.3)
B	8.1	(6.7, 9.6)	2.1	(1.3, 3.0)
Hispanic	14.9	(10.0, 26.9)	3.0	(0.9, 6.0)
Native American	10.8	(7.5, 14.6)	2.3	(0.8, 4.4)
Asian	10.5	(7.9, 13.3)	3.3	(0.9, 6.1)

*CI indicates confidence interval.

weight were used to calculate the body mass index (in kilograms per square meter) as an indicator of actual body size and weight status. The distribution categories of body mass index were obtained from the National Health and Nutrition Examination Survey.¹⁵

Table 4.—Relative Risks of Inappropriate Eating and Weight Loss Behaviors and Body Image Concerns Among Adolescent Chronic Dieters Compared With Other Adolescents*

	Female Subjects				Male Subjects			
	Chronic Dieters, %	Others, %	RR	95% CI	Chronic Dieters, %	Others, %	RR	95% CI
Feel overweight	75.7	38.4	1.97	(1.91, 2.03)	42.7	16.3	2.62	(2.18, 2.97)
Poor body image	44.2	14.7	3.01	(2.83, 3.20)	13.1	4.7	3.86	(3.06, 4.84)
Self-induced vomiting weekly or more	11.9	1.2	9.92	(8.45, 11.64)	4.7	0.5	9.40	(5.61, 15.74)
Use of laxatives to lose weight	7.9	1.1	7.18	(5.83, 8.85)	4.4	0.4	11.00	(6.44, 18.80)
Use of ipecac to lose weight	2.5	0.3	8.33	(3.13, 22.18)	1.1	0.1	11.00	(3.71, 32.65)
Use of diuretics to lose weight	7.3	1.0	7.30	(5.86, 9.09)	2.7	0.2	13.50	(6.67, 27.32)
Ever been on food binge	54.8	26.4	2.08	(1.98, 2.18)	27.7	12.3	2.25	(1.90, 2.67)
Fear of uncontrolled eating	42.7	13.7	3.12	(2.92, 3.33)	18.2	4.1	4.44	(3.52, 5.59)
Binge eating and fear of uncontrolled eating	32.2	8.7	3.70	(3.47, 3.95)	11.0	1.9	5.79	(2.26, 14.84)
Self-reported weight for height <25th percentile BMI	13.1	22.6	0.58	(0.51, 0.66)	11.9	16.2	0.74	(0.54, 1.00)
25th-75th percentile BMI	63.9	60.7	1.05	(1.02, 1.09)	49.0	56.4	0.87	(0.77, 0.98)
>75th percentile BMI	23.0	16.7	1.38	(1.26, 1.51)	39.0	27.3	1.43	(1.24, 1.65)

*RR indicates relative risk; CI, confidence interval; and BMI, body mass index.

Two types of analyses were performed. First, demographic characteristics of chronic dieters were described. Proportions of chronic dieters and 95% confidence intervals were calculated within categories of grade,¹ geographic location, and parental SES. Because many of the proportions were extremely small, the arc sine transformation for proportions was used to calculate confidence intervals.¹⁶

Second, chronic dieters were compared with other adolescents in terms of feeling overweight, poor body image, weekly self-induced vomiting, food bingeing, and use of laxatives, ipecac, or diuretics to lose weight. For boys and girls separately, the risks of having a particular characteristic among chronic dieters were compared with the risks of having that characteristic among adolescents not considered chronic dieters. Relative risks were calculated, and 95% confidence intervals were calculated with Taylor's Series Approximation.¹⁷

For each analysis, the actual sample size varied slightly depending on the number of missing values for each variable. Table 2 presents the numbers and proportions of youth included, according to key characteristics.

RESULTS

The percentages of chronic dieters according to grade in school, location, parental SES, and ethnicity are presented in Table 3. The percentages of chronic dieters among the female adolescent group are five to more than seven times greater than corresponding rates among male adolescents. Among both female and male adolescents, chronic dieting is more frequent in grades 9 through 12 than in the lower grades, but its reported occurrence does not increase appreciably after grade 9. There are small but detectable differences among geographic locations in occurrence of chronic dieting among girls but not among boys. Girls in suburban schools have the highest percent of chronic dieters (13.8%), followed by those in rural (12.5%) and urban (11.1%) settings. Female youth from low SES have greatly elevated frequency of chronic dieting compared with their male counterparts but have slightly, though significantly, lower rates than other

female youth of moderate or high SES. No differences among boys according to SES are apparent. Black girls had the lowest prevalence of chronic dieting compared with other ethnic groups. No differences existed among boys in the different racial groups.

The relative risks for inappropriate eating and weight-loss behaviors, concerns about body image, and body mass index status among chronic dieters compared with other adolescents are presented in Table 4. Chronic dieters are more likely to report other maladaptive eating behaviors compared with those teenagers who are not chronic dieters. Although the percent of chronic dieters was much higher for female adolescents, both male and female chronic dieters exhibit similar risk behaviors. Both male and female chronic dieters were about twice as likely as other adolescents to report binge eating. Three times as many female and five times as many male chronic dieters reported binge eating combined with the fear of not being able to stop eating. Female chronic dieters were seven to nine times more likely to report purging behaviors (ie, vomiting, laxative, diuretic, or ipecac use) for weight control relative to other adolescent girls. Chronic dieters were also more likely to feel overweight and have a poor body image. While there was a much smaller proportion of adolescent male chronic dieters compared with female chronic dieters, male dieters were 11 to 13 times more likely than male nondieters to purge to control their weight and nine times more likely to report vomiting on at least a weekly basis.

COMMENT

We found that dieting is a common occurrence among adolescent girls, with almost two thirds reporting having been on a diet during the previous year. This finding agrees closely with findings of other recent studies.^{1,8,13,18,19} In the survey by Johnson et al,⁹ 14% of teen-

age girls were chronically dieting, which was consistent with our finding that 12% of Minnesota girls were chronic dieters.

Our results are also similar to those of previous studies^{4,8,10,18} in that large and significant gender differences were found. We found that for all the aspects of chronic dieting, eg, inappropriate eating, weight-loss behaviors, and body image concerns (Table 4), the rates of occurrence were greater in girls than boys. This gender disparity has frequently been explained by sociocultural variables that equate thinness with greater attractiveness and social approval. Numerous reports suggest that these social norms are applied more strongly to women than men.^{6,7} The cultural overemphasis on thinness and weight may predispose young women to excessive dieting and abnormal eating patterns.⁷

Although more young women are affected by dieting behaviors, it is important that boys not be overlooked. While the number of male chronic dieters is small ($n=364$), they were nine to 13 times more likely to use unhealthy weight-reduction techniques compared with other male adolescents, and their likelihood of bingeing and experiencing uncontrolled eating was four to five times greater. Therefore, a small but significant portion of adolescent male chronic dieters show evidence of disturbed eating and weight-loss patterns.

We found that the percentage of chronic dieters was significantly lower in school grades 7 and 8 than in grades 9 through 12. From a developmental perspective, teenagers in their middle adolescent years may be more conscious of appearance, weight, and peer opinions than in the early adolescent years. The major increase in subcutaneous and total body fat during puberty in girls may lead to perceptions of being overweight and weight-loss attempts. For both the male and female adolescents in our study, the occurrence of chronic dieting did not increase appreciably after grade 9, suggesting that prevention efforts may need to be established well before this time.

We found few appreciable SES or location (urban, suburban, or rural) differences in the prevalence of chronic dieting for either boys or girls, suggesting that these behaviors have permeated all levels of social status and locations of residence. While the vast majority of studies on the prevalence of dieting and weight-control practices have been conducted in urban areas, one recent study²⁰ of 547 teenage girls from a rural community found that extreme dieting behaviors and symptoms associated with bulimia nervosa were fairly common, with a prevalence of bulimia of 1.7%. Similar to nonurban areas, low social class has been underrepresented in the majority of studies on weight-reducing behaviors and bulimia. Still, the majority of studies^{18,21} have not found social class to be a correlate of bulimia in adolescents.

Few studies have examined ethnic differences in dieting practices. We found that black girls were less likely to diet compared with white girls. Other investigators²²⁻²⁴ have also reported that black teenage girls were less likely to think about their weight or diet compared with white adolescent girls and that bulimia is less common in black teenage girls. Some authors have speculated that there may be differing cultural attitudes toward weight and standards of beauty and that the black culture may be more tolerant of higher weight levels and less likely than whites to equate attractiveness with thinness.^{22,23} We found no significant differences in the prevalence of

chronic dieting among white, Hispanic, Native American, or Asian female adolescents. However, there is a conspicuous gap in the literature on dieting and eating behaviors among these different ethnic groups.

Our data indicate that chronic dieters were more likely to be heavier or of normal weight than were those who were not chronic dieters. Although both male and female chronic dieters were significantly heavier than other students, the relative risks were not large. Several other studies¹⁻³ have found that adolescent boys and girls who diet tend to be heavier than other adolescents. Killen et al¹⁰ found that young male adolescent purgers were heavier and had greater triceps skinfold thickness than nonpurgers, but there was no corresponding difference among girls. There is a major limitation to the use of self-reported heights and weights for adolescents, as few validity studies have been performed. It may be that overweight teenagers underestimate their weight or that young teenagers or those in a rapid phase of growth might not know their actual weights or heights.

Our findings suggest that dissatisfaction with weight and a poor body image are much more pronounced among adolescent chronic dieters than in other teenagers. In addition, chronic dieters are more likely to experience abnormal eating patterns and to engage in unhealthy weight-loss methods compared with other teenagers. While the overall percentage of chronic dieters using purging techniques tended to be small ($<12\%$), the relative risks associated with these behaviors were very high, with chronic dieters being seven to 13 times more likely to use these methods compared with other teenagers (relative risks >2 are considered strong relationships).

Our data indicate a strong relationship between excessive dieting and symptoms associated with bulimia (binge eating and purging techniques). This relationship has been noted in other studies. Wardle¹⁹ found that the incidence of binge eating was much higher among dieting than nondieting medical students. Johnson et al⁹ found that 47% of bulimic students were chronic dieters in contrast to 9% of the nonbulimic group. In his study of 895 male adolescents, Moore² found that there was a higher prevalence of binge eating among boys who wanted to lose weight or were dissatisfied with their weight compared with other boys.

Our results indicate that chronic dieting is not a benign or innocuous process and that associated with it are considerable risks for unhealthy eating and weight-control behaviors. Weight-reducing attempts are important in that these behaviors can become self-perpetuating and appear to be a risk factor for the development of eating disorders. While only a minority of chronic dieters will likely develop the clinical syndromes of anorexia nervosa or bulimia nervosa, the larger group may have health effects from chronic dieting. Health hazards associated with weight-reduction attempts for teenagers include retardation of physical growth, menstrual irregularities, weakness, persistent irritability, constipation, poor concentration, sleep difficulties and impulses to binge eat.^{25,26}

One of the most important findings from our study is that chronic dieting may serve as a screening marker for more severe eating and weight-reduction behaviors. In a clinical setting, asking how often the adolescent diets may help to identify those who are engaging in unhealthy methods of weight regulation or those who may have an eating disorder. Therefore, clinicians involved in health

assessments of adolescents should inquire about dieting practices. If the patient is dieting or has a history of repeated dieting, further history should be obtained on methods of weight control and eating practices.

Finally, efforts are needed in school, health care settings, and the community to provide appropriate education and guidance, especially for preadolescent and adolescent girls. Information should be provided about the normal changes during puberty and the increased deposition of fat tissue. Efforts should be directed toward helping adolescents adopt healthy eating and exercise habits, understanding the physiologic and psychological effects of food restriction and chronic dieting as well as discouraging drastic weight-loss techniques.²⁷ Such education should begin before grade 9.

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The Effect of Valproic Acid on Plasma Carnitine Levels

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● Plasma total, free, and acyl carnitine levels were determined in four groups of children: (1) those treated with valproic acid as monotherapy ($n=43$), (2) those treated with valproic acid plus other antiepileptics as polytherapy ($n=91$), (3) those treated with other antiepileptic drugs alone ($n=43$), and (4) normal patients ($n=89$). The mean free carnitine level was significantly lower in both the valproic acid monotherapy ($29.9 \mu\text{mol/L}$) and polytherapy ($21.4 \mu\text{mol/L}$) groups compared with normal subjects ($36.8 \mu\text{mol/L}$); it was also significantly lower than that in patients treated with other antiepileptic drugs ($36.7 \mu\text{mol/L}$). Comparison of valproic acid polytherapy and monotherapy yielded significantly lower free carnitine levels in the polytherapy group. The ratios of acyl to free carnitine for monotherapy (0.41) and polytherapy (0.45) were significantly higher than that in the normal group (0.25). This study indicates that a general decrease in the carnitine pool should be anticipated in patients taking valproic acid polytherapy and, to a lesser degree, monotherapy. Carnitine levels in the group taking other drugs did not differ from normal.

(AJDC. 1991;145:999-1001)

Valproic acid (VPA) is a branched-chain aliphatic acid, 2-*n*-propylpentanoic acid, commonly used as an antiepileptic drug in the United States since 1978.¹ An effective anticonvulsant for a broad spectrum of epileptic disturbances, valproic acid continues to increase in use, especially in lower-risk patient groups.²

Valproic acid is safe relative to the problems it is used to treat, but clinical experience indicates that patients receiving valproic acid exhibit a variety of side effects. Three important observations relate valproic acid and carnitine. First, complications of valproic acid therapy and carnitine deficiency both mimic Reye's syndrome.^{3,4} Second, valproic acid is toxic to isolated liver mitochondria, with effects similar to accumulating acyl-coenzyme A compounds. Demonstration of carnitine's ability to prevent in vitro mitochondrial toxic effects led to the hypothesis that

carnitine converts acyl-coenzyme A compounds to less toxic acylcarnitine derivatives.⁵ Finally, valproylcarnitine is excreted in urine of patients receiving valproic acid.⁶ Millington et al⁶ hypothesized that the synthesis and subsequent excretion of valproylcarnitine could contribute to the development of carnitine deficiency in valproic acid-treated patients. However, analysis of urine concentrations does not yield valproylcarnitine as the predominant acylcarnitine excreted by valproic acid-treated patients.

The impact of anticonvulsants on carnitine levels has been explored since first addressed by Ohtani et al in 1982.⁴ Carnitine level is lower in patients treated with valproic acid as a monotherapy than in controls.⁷ Patients treated with valproic acid and other anticonvulsants as polytherapy reportedly have lower carnitine levels than patients receiving valproic acid monotherapy⁸ and/or control patients.⁸⁻¹¹ Decreased carnitine levels may also follow treatment with other antiepileptic drugs (OADs) alone.^{12,13}

Some investigators have not found differences in free carnitine levels between patients treated with OADs and controls^{4,10} or between patients given valproic acid monotherapy, those treated with OADs, and controls.^{8,11} Other studies finding decreased free carnitine levels did not divide patients receiving valproic acid into monotherapy and polytherapy subgroups.^{4,12-16} Generally, most studies involved small samples of valproic acid-treated patients and/or patients older than 3 years.^{4,7-10,12,13,15,16} We assessed the effect of therapy with valproic acid monotherapy, valproic acid polytherapy, and OADs on the plasma carnitine pool between all four groups (including a normal group for comparison) in a relatively large population of pediatric-age patients.

PATIENTS AND METHODS

A total of 266 patients had plasma total, free, and acyl carnitine levels determined. The four groups were as follows: (1) patients treated with valproic acid monotherapy ($n=43$), (2) patients treated with valproic acid polytherapy ($n=91$), (3) patients treated with OADs ($n=43$), and (4) normal, healthy patients who served as controls ($n=89$). The groups of patients treated with anticonvulsants (valproic acid monotherapy, valproic acid polytherapy, and OADs) included 26, 48, and 19 female patients and 17, 43, and 24 male patients, respectively. The normal group had 47 female patients and 42 male patients. The mean age of the patients treated with valproic acid monotherapy was 8.1 years (range, 1.3 months to 20.3 years); of those treated with valproic acid polytherapy, 8.2 years (1 month to 21.6 years); of the OAD

Accepted for publication April 22, 1991.

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Plasma Carnitine Total, Free, Ester, and Ratio Levels in Patients Treated With Monotherapy, Polytherapy, and Other Antiepileptic Drugs and in Normal Subjects

Group	n	Carnitine, $\mu\text{mol/L}$			
		Total	Free	Ester	Ester-Free Ratio
Valproic acid monotherapy	43	40.8* \pm 14	29.9† \pm 10	10.9‡ \pm 9	0.41§ \pm 0.5
Valproic acid polytherapy	91	29.3 \pm 14	21.4 \pm 12	8.0 \pm 4	0.45¶ \pm 0.3
Other antiepileptic drugs	43	48.1 \pm 11	36.7 \pm 10	11.5 \pm 7	0.34 \pm 0.3
Normal subjects	89	44.2 \pm 10	36.8 \pm 7	8.9 \pm 5	0.25 \pm 0.1

* $P < .05$ vs other antiepileptic drug, $P < .01$ vs valproic acid polytherapy. All values expressed as mean \pm SD.

† $P < .01$ vs normal subjects, $P < .01$ vs other antiepileptic drugs, $P < .01$ vs valproic acid polytherapy.

‡ $P < .05$ vs valproic acid polytherapy.

§ $P < .05$ vs normal subjects.

|| $P < .01$ vs normal subjects, $P < .01$ vs other antiepileptic drugs.

¶ $P < .01$ vs normal subjects.

group, 8.3 years (1.4 months to 17.1 years); and of the normal subjects, 6.7 years (1.3 months to 17.2 years). Mean age differences between the four groups were not significantly different by analysis of variance procedure.

Patients receiving anticonvulsants (valproic acid monotherapy, valproic acid polytherapy, and OADs) were treated for different types of epilepsy. The OADs included carbamazepine ($n = 18$), phenobarbital ($n = 10$), phenytoin ($n = 9$), and ethosuximide ($n = 1$) as monotherapy or in combinations ($n = 5$). Patients were selected for determination of plasma carnitine level from the practices of two pediatric neurologists on the basis of one of the specific drug regimens. Blood samples were randomly drawn after initiation of valproic acid and OAD therapy, with a minimum elapsed time of 5 days. Plasma samples from the valproic acid monotherapy and polytherapy groups were obtained from 1984 to 1990, and from the OAD group, between 1986 and 1990.

All samples were collected at Valley Children's Hospital, Fresno, Calif, and frozen plasma was sent to the Metabolic Analysis Laboratories Inc in Madison, Wis. Plasma carnitine levels were assayed by the method of Parvin and Pande.¹⁷ In most cases, only one level was available after the introduction of valproic acid therapy but before carnitine supplementation. Occasionally, however, more than one level was available as a result of clinical laboratory orders. The lowest free level was selected, and this almost always corresponded to the last available level before carnitine supplementation. Of note, this supports other findings of a dose-response (ie, time-dependent) relationship. Patients with a known metabolic disorder were excluded. The nonretrospective portion of this study, plasma level determination in normal subjects, was approved by both the Valley Medical Center Human Investigation Review Committee and the Valley Children's Hospital Human Subjects Committee. Informed consents were obtained from either the patient or the parent/guardian if the patient was a minor.

RESULTS

Mean total, free, and esterified plasma carnitine levels and the esterified-to-free carnitine ratio are presented for the four groups in the Table. Data for the four different groups and four variables were analyzed by means of a one-between multivariate analysis of variance procedure. Post hoc tests were performed on resultant univariate analyses by Scheffe's procedure.

The mean total carnitine level was significantly lower only in patients given valproic acid polytherapy compared with normal subjects. However, the levels in both the valproic acid monotherapy and polytherapy groups were significantly lower than those in the OAD group ($P < .05$ and $P < .01$, respectively). In addition, the mean total carnitine level in the valproic acid polytherapy group

was significantly lower than that in the valproic acid monotherapy group ($P < .01$).

The mean free carnitine level was significantly lower in both the valproic acid monotherapy and polytherapy groups than in the normal subjects ($P < .01$ for both) and also significantly lower than in the OAD group ($P < .01$ for both). Comparison of valproic acid polytherapy and valproic acid monotherapy also yielded a significantly lower plasma free carnitine level ($P < .01$).

The mean acylcarnitine level was significantly lower in patients receiving valproic acid polytherapy than in those receiving OADs ($P < 0.01$) and also was significantly lower than that in the group receiving valproic acid monotherapy ($P < .05$).

The ratio of acylcarnitine to free carnitine levels was significantly higher in both the valproic acid monotherapy and valproic acid polytherapy groups than in the normal subjects ($P < .05$ and $P < .01$, respectively).

COMMENT

Our study supports previous findings that administration of valproic acid results in a lowering of carnitine levels.^{3,4,7-15} Both groups of our patients receiving valproic acid had plasma free carnitine levels significantly lower than those of patients receiving OADs and controls; moreover, plasma free carnitine levels in the valproic acid polytherapy group were significantly lower than those in the valproic acid monotherapy group.

In contrast to our data, Laub et al,¹⁰ Komatsu et al,⁸ and Beghi et al¹¹ did not find the free carnitine levels in the valproic acid monotherapy group significantly lower than those in the controls. Only Komatsu et al⁸ found, as we did, a significant difference between free carnitine levels in the valproic acid polytherapy and valproic acid monotherapy groups. Consistent with the findings of Ohtani et al,⁴ Laub et al,¹⁰ Komatsu et al,⁸ and Beghi et al,¹¹ we did not find significant differences in free carnitine levels between the OAD and normal groups, suggesting that reduction of plasma carnitine level is associated with valproic acid therapy but is not associated with antiepileptic therapy in general. Moreover, the lowest mean free carnitine level during valproic acid polytherapy in comparison with the valproic acid monotherapy, OAD, and normal groups suggests that treatment with valproic acid in combination with antiepileptic drugs other than valproic acid increases the reduction of carnitine level.

Valproate and Carnitine—Opala et al

In general, carnitine deficiency should be anticipated in patients taking anticonvulsant medications that include valproic acid (particularly if these medications induce mitochondrial enzyme systems); why the lowest plasma free and total carnitine levels were found in the group treated with valproic acid polytherapy remains speculative. It is likely that drug interactions can lead to enhanced valproic acid metabolism and further impairment of carnitine values. This is particularly true of phenobarbital, which may result in increased conversion of valproic acid to toxic metabolites.¹¹ Another possibility is that patients receiving polytherapy are more severely neurologically affected and may have an underlying metabolic disorder predisposing them to carnitine deficiency.

It is also important to consider alternative mechanisms of decreasing plasma free carnitine level during valproic acid therapy. Suggestions from other investigators include increased renal loss of free carnitine,^{18,19} insufficient endogenous carnitine synthesis, or a decreased dietary carnitine intake.⁷

Thoughtful analysis of the relationships among the variables and cited hypotheses may yield some insight into an overall mechanism of valproic acid-induced decreased carnitine levels. Significantly lower acyl, free, and total plasma carnitine levels in valproic acid polytherapy in comparison with valproic acid monotherapy indicate that the total carnitine pool in the valproic acid polytherapy group of patients is significantly decreased. Also, ratios of acyl to free carnitine in both valproic acid monotherapy and valproic acid polytherapy groups were the same and significantly higher than in normal subjects. These observations are in agreement with the hypothesis that (1) elevated production of acylcarnitine increases the excretion of acylcarnitine; (2) this reduces the free carnitine level^{6,9}; and (3) the decreased free carnitine level results in a relative increase in acylcarnitine level, compared with the free carnitine level, which constitutes an increase in the acyl-free carnitine ratio.

It is also important to evaluate overall findings in the context of methodologic considerations. Differences in levels of esterified carnitine in our data may be due to varying durations of therapy before carnitine assay. In addition, elevated urinary excretion of acylcarnitines during an initial period of valproic acid administration leads to insufficient quantities of ingested and endogenously produced carnitine necessary to maintain tissue and plasma stores at normal levels¹⁶; later, as free carnitine levels become low, esterified carnitine levels may also decrease because of inadequate free carnitine available to combine with acyl groups.

The absence of carnitine determinations before valproic acid therapy leads to the possibility that low carnitine levels may have preexisted in the population. Indeed, the low free carnitine levels in the group treated with valproic acid polytherapy, instead of the preferred monotherapy, coincide with the group we expect to present the most difficult seizure control problems and therefore be the most involved neurologically. However, the absence of a significant difference between the OAD and normal groups indicates that the patient sample did not have low carnitine levels before therapy.

CONCLUSION

The sample size of the four groups of patients in our study, valproic acid monotherapy, valproic acid polyther-

apy, OADs, and normal, allows for establishment of reliable statistics indicating that a general decrease in the carnitine pool should be anticipated in patients taking valproic acid polytherapy and, to a lesser degree, valproic acid monotherapy. Carnitine levels in the OAD group did not differ from normal.

This research was supported in part by a grant from Sigma Tau Pharmaceuticals Inc, Gaithersburg, Md.

We to thank the University of California, San Francisco, library staff for their support; the Valley Children's Hospital laboratory staff, Tim O'Hara, and Steven Szabo-Aczel, MD, for project consultation; and Any Szabo for data compiling.

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Support Services for Pediatric Trainees

A Survey of Training Program Directors

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• We conducted a survey of pediatric training program directors (75% response rate) regarding program support services for house staff, directors' attitudes about stress in training, and program plans to ameliorate such stress. Support services included explicit measures to alleviate stress, policies that may minimize stress, evaluation of house staff performance, feedback regarding career concerns, and benefits (eg, medical insurance and child care). Most programs offered services to reduce stress from training, but few offered preventive services. Support policies were reported to be inadequate, especially in the areas of coverage for leaves of absence. Maternity leave represented most leaves of absences, as 10% of the female house staff and 11% of the male house staff members became parents. Program directors' terms were short, and only 30% perceived these roles to be their primary roles. Male directors believed that female house officers had a harder time adjusting to their programs. We suggest changes and present a simple way for program directors to evaluate their support services.

(AJDC. 1991;145:1002-1005)

Stress in postgraduate medical training concerns training directors, trainees, and the general public. Many support services to reduce stress in training have been proposed, but information about these services in pediatric training programs is lacking.¹⁻⁸ A committee of program directors of internal medicine has outlined what services should be included in a supportive program.⁹ Berg and Garrard¹⁰ have categorized support services available in family practice programs. Our study was designed to document support services offered in pediatric training programs.

MATERIALS AND METHODS

A questionnaire was developed that addressed several topics and included both closed- and open-ended questions. A test questionnaire was sent to six pediatricians who were either training directors or involved in pediatric education. Information

was solicited about the services available to reduce stress (Table 1). The study population included every training director (n=232) in an accredited pediatric training program on July 1, 1987, from a list provided by the Association of Pediatric Program Directors.

There were two mailings separated by 4 weeks. Eight programs were excluded from the original 232 because they had merged with other programs or were no longer training pediatricians. Sixty-one percent of the responses came from the first mailing and another 14% from the second, for a total response rate of 75%. Data from both mailings were combined. The only difference between data from the two mailings was that respondents to the second mailing spent more time (30%) functioning as training directors ($P<.05$) and had been in the position less time (4 years or less) ($P=.01$) than directors responding to the first mailing.

Demographic data included program affiliation, the presence of a designated training director, gender of director, number of years as training director, and percentage of time spent fulfilling duties as training director. Inquiries were made about number and gender of the trainees, number of leaves of absence, number of pregnancies, and number of referrals for counseling during the training year. Training directors were asked about their attitudes toward support services, and responses were coded using a 5-point Likert Scale.

Department Editors.—Hugh D. Allen, MD, Columbus, Ohio; Fredric Buig, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—Bergman and Adler present a survey of program directors that addresses management of house officer stress. Most directors deal with crises, but few deal with problems through prevention. The authors discuss various problems and offer a way for programs to evaluate their support services. This is a good start.—H.D.A.

Accepted for publication December 14, 1990.

From the Department of Psychiatry, Stanford (Calif) Medical School (Dr Bergman), and Childrens Hospital of Los Angeles (Calif) and the UCLA School of Medicine (Dr Adler).

Reprints not available.

Support Services for Pediatric Trainees	
Pediatric Support Service	% of Pediatric Training Programs Reporting Services
Explicit measures to alleviate stress	
Orientation	98
Social events	98
Psychiatric services	92
Specific counseling for stress	61
Retreats	44
Counseling for house staff member's families	53
Support groups	35
Ombudsman	30
Drug/alcohol education	33
Supportive policies to minimize stress	
Maternity leave policy	95
Ward on-call—every 4th night or less frequently	49
NICU on-call—every 4th night or less frequently	40
House staff goes home after call before 5 pm	31
Limit on maximum consecutive hours worked	30
More than 4 weeks of vacation for all years	28
Coverage by faculty and house staff	12
Evaluation and feedback	
Evaluation of house staff	100
Feedback from house staff to faculty	92
Disciplinary policy and grievance procedure	88
Review of program	84
Career counseling	80
Faculty advisor	77
Benefits	
Medical insurance	100
Mental health insurance	89
Disability coverage	81
Payment for counseling	52
Child care	19

RESULTS

Our data on characteristics of the respondents were compared with data available about pediatric training programs from the American Medical Association's 1988-1989 *Directory of Graduate Medical Education Programs*.¹¹ There was no difference between the two groups of data in geographic distribution or percentage of women house staff members.

Characteristics of Program Respondents and Trainees

Most programs were university based (101 [45%]) or affiliated (90 [40%]). The remaining 33 programs included

those that were not university affiliated and those that were affiliated with military bases or religious institutions. Size was associated with affiliation; the largest programs were university based. Seventy-eight programs (35%) had 17 or fewer house staff members, 70 (31%) had 18 to 35 house staff members, and 76 (34%) had 36 or more house staff members. Sixty-seven program directors (30%) reported that house staff members trained in only one hospital; 76 (34%), two hospitals; 63 (28%), three hospitals; and 18 (8%), four or more hospitals.

Most programs (217 [97%]) had a designated program director, 65 (30%) of whom were department chairs and 22 (10%) of whom had another title related to training (eg, residency manager). Only 65 (30%) considered themselves primarily program directors. Forty-seven respondents (21%) were women. Half of the respondents graduated from medical school before 1968, and half spent 30% or less time in their roles as program directors. Half were program directors for 4 years or less.

The survey comprised 4424 house staff members, 2300 (52%) of whom were women. This is consistent with the ratio reported in the American Medical Association's 1988-1989 *Directory of Graduate Medical Education Programs*.¹¹

How Supportive Are Pediatric Training Programs?

We inquired about explicit measures to alleviate stress in residency training programs. Social events and orientation programs were nearly universal (220 [98%]). Almost half (99 [44%]) of all programs had retreats for house staff. The majority of the retreats were for postgraduate-year-1 interns alone. In most programs, a variety of individuals ran the retreat, including chief residents, faculty, and consultants. A smaller number (78 [35%]) of responding programs offered support groups, of which 17 (22%) were run by faculty and nine (12%) by consultants. Only 23 program directors (29%) who offered support groups perceived them as helpful. Individual counseling was available in 206 programs (92%), and specific psychiatric services directed to issues of stress in residency training were offered by 137 programs (61%). Family counseling was offered by 119 programs (53%), and an ombudsman was available in 74 programs (30%). Only 74 programs (33%) provided drug and alcohol abuse education.

Two hundred six programs (92%) offered counseling for house officers. In 90 programs (44%), it was provided by the psychiatric staff of the training program. Counseling in the remaining 116 programs was provided by the program director (24 programs [21%]), behavioral science staff (14 programs [12%]), employee assistance programs (12 programs [10%]), private psychiatric and pastoral counselors (six programs [5%]), and social workers and behavioral pediatricians (11 programs [5%]). Directors of the remaining programs did not note who provided counseling. Between 1987 and 1988, 106 house staff members (2.4%) were referred to counseling owing to poor performance.

We also explored on-call schedules. On-call duties every fourth night or less often for ward rotations were reported by 110 respondents (49%). On-call duties of similar frequency, but for rotation into the neonatal intensive care unit, were reported by 90 respondents (40%). Sixty-nine programs (31%) sent house staff members home around or before 5 pm the night after being on call, and 67 programs (30%) limit the maximum number of consecu-

tive hours worked to 32. Half the programs reported that their house staffs worked 33 to 39 consecutive hours, and 45 respondents (20%) said there was no limit on work hours.

Coverage for absent house staff members was most often provided by other house staff members (179 programs [80%]) or occasionally by a mixture of faculty and other house staff members (27 programs [12%]). In one program, the faculty alone covered for absent house staff members. A maternity leave policy was in place in 213 programs (95%), and time off ranged from less than 6 weeks (98 programs [46%]) to 8 weeks, to 3 months (38 programs [18%]). From 1987 to 1988, 230 female house staff members (10%) and 233 male house staff members (11%) became parents. Most programs (134 [60%]) had leave of absence policies, and 110 programs (49%) granted at least one leave of absence during the year. Of these leaves of absence, 30 (27%) were maternity leaves, 12 (11%) were because of personal stress, six (5%) were because of family illness, and 8 (7%) were because of personal illness. No significant correlations were noted between leaves of absence and characteristics of the program, the director, or trainees. All programs had specific vacation policies, and 63 (28%) offered 4 or more weeks of vacation for all years of training. A shared-residency program was offered by 65 programs (29%), but of those only four (6%) had individuals actually in a shared residency.

Written disciplinary policies were provided by 199 programs (89%), feedback to faculty by 206 (92%), faculty advisers by 172 (77%), specific career counseling by 179 (80%), and a committee to review the program by 188 (84%).

Medical insurance was offered to house staff by all programs, mental health insurance by 199 (89%), and disability insurance by 181 (81%). Specific payment for counseling was reported by most programs (107 of 206 [52%]), and a few programs (43 of 206 [19%]) offered child care.

We explored one tangential measure of stress by asking why house staff members left their training programs. Sixty-six house officers (29%) had left their programs unexpectedly. Of the house staff members who left, 45 (69%) changed their specialties, seven (10%) left because of family reasons, five (7%) left because of illness, and the rest (nine [14%]) reportedly left because of religious reasons, feelings of inadequacy, and other reasons.

Program Directors' Attitudes Toward Training

A series of questions was asked of the program directors exploring their attitudes toward support services. Most training directors (201 [90%]) believed that house staff support was a priority in the program, that their house staff members were happy with the program, and that the patients benefited from house staff support services. Training directors who believed that house staff support was a priority in their programs also believed that support programs helped recruitment ($r=.35$ and $P=.0001$). To a lesser degree, they believed that access to support services made trainees better pediatricians (181 respondents [81%]) and that the faculty generally cared about the house staff. One hundred fifty-nine respondents (71%) believed their programs provided more support than other programs. Only 83 program directors (37%) believed that house staff training was easier now

than when they were in training, and half believed that the house staff worked too many hours per week. Most directors (130 [58%]) believed that female house staff members should be able to plan a pregnancy during training, and 58 (26%) believed that, in general, female house staff members had a harder time adjusting to training than did male house staff members.

The training directors noted the following greatest sources of stress among house staff members (some respondents listed more than one item): workload (72 [32%]), caring for very sick or difficult patients (60 [27%]), conflicts between work and home life (54 [24%]), high expectations of themselves (25 [11%]), concern about lack of knowledge (18 [8%]), work relationships (nine [4%]), money (seven [3%]), and quality of teaching (two [1%]). In response to an open-ended question, 40 program directors (18%) anticipated making the program more supportive, reducing the number of working hours, or planning a retreat. A small percentage (20 respondents [9%]) were planning to encourage more faculty involvement, while 13 respondents (6%) were planning to add an advisory system.

Program directors were also asked about recruitment. Slightly over half the programs (114 [51%]) had increasing numbers of applicants, 25 (11%) had decreasing numbers of applicants, and 85 (38%) had stable levels of applicants. One hundred fifty programs (67%) recruited enough residents to fill all their positions, 27 (12%) had one vacant position, and 47 (21%) had two vacant positions.

COMMENT

This study describes a way to measure the level of house staff services that may reduce stress in pediatric training programs. Program directors may not wish to include the specific services listed, but this data makes comparisons of the programs with a 1988 national data base possible. These comparisons may be helpful in discussions with hospital administrations regarding the institution of new services.

Although this study mostly catalogs existing programs and services, some interesting observations can be made. Those services required by the Accreditation Council for Graduate Medical Education were almost universally provided. Others, such as social events and orientation, were also offered by all training programs. Availability of services to reduce or help cope with the stress of the program showed an interesting pattern. While 92% of the programs offered various counseling options for treatment of stressed house staff members, preventive measures such as support groups and retreats were offered by only 78 programs (35%) and 99 programs (44%), respectively. Fewer than one third of the directors whose programs offered support groups thought that they were helpful. Although there is considerable concern regarding physician impairment due to chemical dependency, only 74 programs (33%) offered alcohol and drug abuse education.

Program directors and the hospital administration set policies for house staff and have considerable control in this area. Despite this, specific policies that might alleviate house staff stress were absent from most programs. Although trainees in 49% of the programs were on call every fourth night or less often, fewer than one third of the programs limited consecutive working hours to less than 32. Four weeks of vacation each year were offered by

28% of programs. Vacation time was distributed unequally through the 3 years of training in most programs, and the largest amount of vacation time was in the later years, although the internship year is clearly the most stressful. Support policies may change in response to legislation, but in most hospitals these policies are under institutional and program control and do not need legislative approval to be reevaluated.

Coverage for absent house staff members was almost exclusively provided by other house staff members. Coverage by faculty and innovative methods of coverage were rare. House staff members' absences are disruptive to all programs and, in light of the data, it becomes increasingly clear that program directors need to plan prospectively for absences, the most common of which is maternity leave. Change in assigned rotations and electives is stressful to the remaining house staff members and can significantly affect the educational program. The program director and administration must explore methods of coverage that do not increase burdens on house staff members.

Most programs had maternity leave policies, but they varied considerably. Ten percent of the female house staff members and 11% of the male house staff members became parents during the year studied. This is consistent with a recent study by Sinal et al¹² in which 11% of 904 female physicians became pregnant during their internships, and 32% became pregnant during their residency programs. Regardless of when their babies were born, 60% had maternity leaves of 6 weeks or less. Parental leave should be planned prospectively and anticipated by program staff. Costs of providing a method to deal with such absences should be included in the budgets of training programs. There will always be exceptional situations for which prospective planning will be inadequate, but house staff members and program directors should plan for what seems to be a consistent use of the leave of absence policy.

The issue of maternity leave also brings up the issue of gender in residency training. More than 50% of trainees in pediatric training programs are women. Only 21% of the program directors were women, and 52% of the pediatric house staff members in our study were women. The attitudes of program directors toward house staff support programs did not differ on the basis of gender, except that male directors believed that female house officers had a harder time adjusting to stress in training ($P = .0004$). The view that female house officers should be able to plan pregnancies during training was equally held by both male and female program directors.

Most training directors perceived that their house staffs were happy with their programs. They considered their training programs to be more supportive than other programs and believed that patients benefited from house staff support services. Another reflection of the program directors' general comfort level with support services was that only 18% of the program directors anticipated adding support services to their programs. Program directors identified the greatest sources of stress among house staff members as workload, caring for sick or difficult patients, and conflict between work and home life. This differed somewhat from a previous report⁸ in which interns stated that fatigue, lack of time for family and personal activities, and making a mistake were the greatest sources of stress.

The role of the program director will need to be reexamined as programs struggle with the difficult issues

of meeting the dual responsibilities of the programs' educational requirements and of the service requirements of their institutions. A consistent and long-term commitment from program directors will allow the examination and achievement of these often conflicting goals and investigation of preventive strategies to reduce stress. Such strategies should include the planning and evaluation of administration policies to reduce stress. A policy that anticipates leaves of absences (including parental leave for male and female house staff members) should be considered by each program, and policies that deal with frequency of on-call duties, number of consecutive working hours, benefits (eg, disability and life insurance), and other issues affecting trainee stress should be evaluated. These issues are under the control of individual program directors and their administrations. Changing policy in an institution often takes a long time, and a consistent spokesperson with a strong support base who advocates for change is necessary. In return, chairmen in pediatrics need to support program directors financially and academically.

This simplified way for programs to evaluate the support services available to their trainees should be a good starting point for directors who are contemplating changes in their programs. It might also stimulate program directors to evaluate the effectiveness of existing services and to explore innovative ways to reduce stress in training programs. Clearly, the ability to provide support services to pediatric residents will provide programs with a competitive edge in an increasingly tight market for potential applicants.

This study was supported in part by a grant from the Childrens Hospital of Los Angeles General Pediatric Research Fund.

We thank Evan Charney, MD, and the Association of Pediatric Training Program Directors for their participation in and support of this survey.

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Optimal Positioning of Endotracheal Tubes for Ventilation of Preterm Infants

Avi Rotschild, MD; David Chitayat, MD; Martin L. Puterman, PhD; Min S. Phang, MB;
Emily Ling, MB, BS; Virginia Baldwin, MD

► Accurate knowledge of upper-airway dimensions is required to prevent malpositioning of endotracheal tubes in preterm infants. We measured vocal cord–carina, oral–carina, and nasal–carina distances in situ at autopsy of two groups of infants (<1000 and ≥1000 g). In all 24 infants, crown–heel length, crown–rump length, and occipitofrontal circumference were better than weight in predicting upper-airway dimensions. Flexion of the neck decreased and extension increased both nasal–carina and oral–carina distances. Lateral rotation produced no significant changes. The postmortem data were not different from nasal–carina distances measured radiologically in 40 living, nasally intubated and ventilated infants, confirming the clinical validity of our findings. Regression equations were derived to predict optimal endotracheal tube lengths based on the external measurements of crown–rump length and crown–heel length.

(AJDC. 1991;145:1007-1012)

With the advent of neonatal intensive care, endotracheal intubation and mechanical ventilation of very-low-birth-weight infants is now common. However, malpositioning of the endotracheal tube (ETT) is still a well-recognized and, unfortunately, frequent complication of mechanical ventilation.^{1,2} To minimize the risk of this complication, accurate knowledge of the upper-airway dimensions is essential. Earlier studies used various methods to measure the dimensions and topographic locations of the important anatomic landmarks in the upper airway and attempted to predict optimal ETT lengths. These methods included anatomic measurements of ex-

cised tissues from autopsies,^{3,4} observations at bronchoscopy in live infants,^{5,6} and radiologic evaluations^{1,2,7-9} that included the effect of respiratory movements¹ and alterations of head position.^{1,10-12} However, few data are available from direct measurements of upper-airway dimensions in neonates, and practically no data are available for infants who weigh less than 1000 g.

Our study was carried out to formulate a reliable method of predicting the optimal ETT length from data obtained from direct measurements of upper-airway dimensions in the neonatal population, including very-low-birth-weight infants, using an in situ postmortem method. We also studied the changes in these dimensions with different head positions. The clinical relevance of the postmortem data was tested by comparing the results of the postmortem study with those obtained radiologically in living, nasally intubated and ventilated infants.

SUBJECTS AND METHODS

Study Population

Postmortem measurements of upper-airway dimensions were performed in 24 infants whose parents had given consents for autopsies and who met either of the following two criteria: (1) nonmacerated stillborn infants over 22 weeks of gestation with birth weights of 400 g or more and (2) infants who died in the neonatal period or during the first 4 months of life. Radiologic determination of nasal–carina (NC) distances was carried out in a separate group of 40 living, nasally intubated and ventilated infants. Infants with hydrops fetalis, congenital malformations, or chromosomal abnormalities or who were small for gestational age were excluded from both study groups.

Postmortem Study

Postmortem crown–heel length (CHL), crown–rump length (CRL), occipitofrontal head circumference (OFC), and body weight were measured before autopsy dissection. To study upper-airway dimensions, the body cavity was entered with the usual Y-shaped incision, and the anterior part of the rib cage was removed. The trachea was then exposed in situ by removing the thymus and dissecting the blood vessels. A short transverse incision was made in the anterior wall of the trachea at the level of the carina. To measure the distances from the carina to the naris and to the upper lip, each infant was intubated alternately nasally and orally with a pediatric suction catheter marked at centimeter intervals (Argyle, Sherwood Medical, Petit-Techain, Belgium). The catheter was advanced to the carina and secured under direct vision at the level of the carina. Nasal–carina and oral–carina (OC) distances were taken as the lengths of the suc-

Accepted for publication February 25, 1991.

From the Division of Neonatology, Departments of Pediatrics (Drs Rotschild, Phang, and Ling) and Medical Genetics (Dr Chitayat), Faculty of Commerce (Dr Puterman), and Department of Pathology (Dr Baldwin), University of British Columbia, B.C.'s Children's Hospital, Vancouver.

Read in part before the Joint Scientific Meeting of the Australian College of Paediatrics and the Singapore Paediatric Society with the Canadian Paediatric Society, Singapore, May 18, 1990; and presented as a poster exhibit at the American Academy of Pediatrics District VIII Perinatal Pediatrics Conference, Keystone, Colo, May 25 to 27, 1990.

Reprint requests to B.C.'s Children's Hospital, Room 1N1, 4480 Oak St, Vancouver, British Columbia, Canada V6H 3V4 (Dr Ling).

Table 1.—Population Description

	Mean \pm SD (Range)	
	Postmortem Study (N = 24)	Radiologic Study (N = 40)
Gestational age, wk		
At birth	31 \pm 6.1 (23-42)	27.7 \pm 3.6 (23-34)
At study	32 \pm 7.2 (23-48)	29.4 \pm 4.5 (23-42)
Weight, g		
At birth	1937 \pm 1365 (415-4920)	1197 \pm 651 (500-3620)
At study	2203 \pm 1628 (415-5355)	1403 \pm 810 (500-3965)
No. of infants weighing <1000 g	9	19
Crown-rump length, cm	32 \pm 8.3 (20-45.5)	26.8 \pm 4.8 (20.4-38.0)
Crown-heel length, cm	45 \pm 10.6 (28.1-62.5)	39.2 \pm 6.2 (30.3-54.0)
Head circumference, cm	31 \pm 6.6 (21.5-43)	26.8 \pm 4.2 (22-37.8)
Vocal cord-carina length, cm	4.1 \pm 1.1 (2.2-6.5)	...
Oral-carina length, cm	9.3 \pm 2.4 (5.8-13.5)	...
Nasal-carina length, cm	10.8 \pm 2.5 (7-15.6)	9.4 \pm 1.5 (6.8-13.9)

tion catheter at the naris and upper lip, respectively, the catheter tip at the carina being 0 cm. These two measurements were taken for each infant in five different positions of the head relative to the body. These positions were the midline neutral, lateral rotation 90° to the right, lateral rotation 90° to the left, maximum flexion, and maximum extension.

To determine the vocal cord-carina (VC) distance, the distance from the thyroid cartilage notch to the carina was first measured in situ with the head in the neutral position. The lungs and trachea were then removed from the body en bloc. The trachea was incised posteriorly longitudinally, and the distance from the thyroid cartilage notch to the vocal cords was measured. The VC distance was obtained by subtracting the distance from the thyroid cartilage notch to the vocal cords from the distance from the thyroid cartilage notch to the carina.

In two of the autopsies, the VC measurement was repeated after the trachea was removed from the thoracic cage.

Radiologic Study

The NC distances were determined in a separate group of living, nasally intubated infants by means of clinical and radiologic data. The nasal route is the preferred route for intubation of infants in our nursery. The ETT length from its tip to the subject's nares was recorded just before or after clinically indicated anteroposterior chest roentgenograms. All chest roentgenograms were performed with the infant's head held in the neutral position and the infant lying directly on the roentgenographic film at a focal film distance of 101.6 cm. Infants with conditions causing displacement of the trachea and main-stem bronchi were excluded from the study. The distance of the ETT tip to the carina was measured on the chest roentgenogram only if the carina and main-stem bronchi were clearly visible and the chest was well centered during exposure. The NC distance was the sum of the ETT length and the ETT tip to carina distance. The magnification on roentgenogram of the ETT tip to carina distance was shown to be negligible by taking roentgenograms at the same focal film distance of a metal grid placed at different distances of up to 5 cm from the film cassette to simulate the different depths of the trachea in infants of different weights.

On the same day, OFC, CHL, CRL, and weight were measured by standard methods. Only one set of measurements was obtained for each subject.

Statistical Analysis

For data from the postmortem study, multiple linear regression was used to investigate the relationship of VC, NC, OC, nasal-midtrachea, and oral-midtrachea lengths with potential predictors, including corrected gestational age, weight at autopsy, CHL, CRL, and OFC. All subset regression with adjusted R^2 criterion was used for model selection. We investigated whether transformations¹³ to logarithmic, polynomial, and piecewise linear (straight lines with different slopes on different ranges of the explanatory variable) functions of explanatory variables produced improved estimates and assessed the quality of the fits by residual analysis. We computed 95% prediction intervals as the predicted value determined by the regression equation $\pm t(n-2, 0.975)$ times the SE of prediction.¹³ Simple regression was used to determine whether the changes in NC and OC lengths due to alterations in head position relative to the body were dependent on the NC and OC measurements with the head in the neutral anatomic position.

Subjects were divided into two groups on the basis of weight at autopsy (<1000 g and \geq 1000 g). Standard univariate methods were used to obtain ranges for the effects of head positioning on the measurements in each group. Measurements in the two groups were compared by means of two-sample t tests adjusted for unequal variances. Effects of position changes within subjects were analyzed by paired t tests. Bonferroni adjustments were taken into account when statistical significance was assessed. For the radiologic study, multiple linear regression was used to investigate the relationship of NC distance with corrected gestational age, weight, CHL, CRL, and OFC and to compare relationships in postmortem and radiologic studies. All statistical calculations were performed with the Number Cruncher statistical software.

RESULTS

Postmortem Study

Postmortem measurements of upper-airway dimensions were performed in 24 infants, whose corrected gestational age at autopsy ranged from 23 weeks to term plus 8 weeks. Nine infants weighed less than 1000 g. The basic descriptors of the study population are provided in Table 1. There was a significant linear relationship between each of the three inner airway measurements and

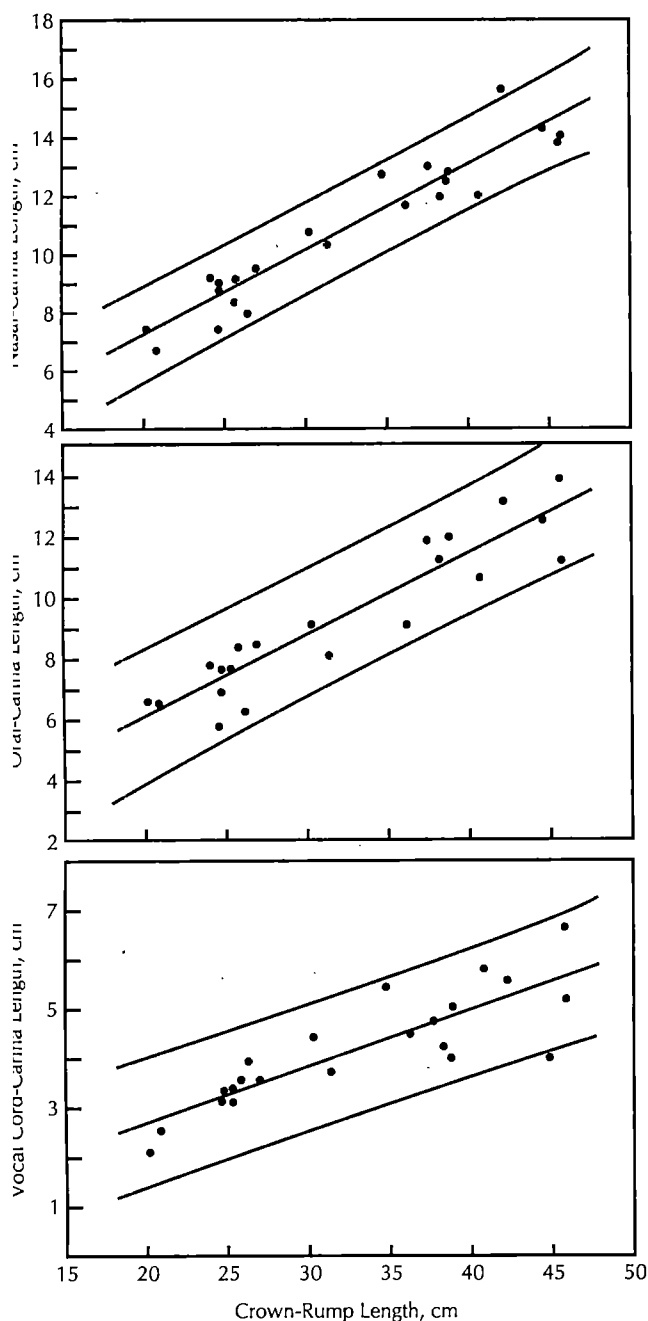


Fig 1.—Relationships of nasal-carina, oral-carina and vocal cord-carina lengths with crown-rump length. Center lines are the regression estimates; outside curves are 95% prediction intervals, based on SEs of prediction. Some points are obscured because of nearly concurrent values.

Each of the four external anthropometric measurements, as demonstrated by the estimation equations (Table 2). We found that the use of polynomials, other transformations, or additional predictor variables did not provide any better explanatory relationship based on the adjusted R^2 criterion and residual analysis.

The CRL was the best single anthropometric measurement for predicting the inner airway dimension for all three upper-airway measurements. The relationships between each of NC, OC, and VC to CRL, together with 95% prediction intervals, are displayed in Fig 1. Corresponding graphs for the relationships of upper-airway measurements with CHL, weight, and OFC are similar and,

therefore, not shown. The CHL and OFC, but not weight, were as good as CRL for predicting upper-airway distances.

The effect of head orientation on NC and OC measurements is depicted in Fig 2. In both weight groups, flexion significantly decreased ($P < .005$) and extension increased ($P < .0001$) OC and NC distances, while left and right rotation did not alter the measurements. We looked at the effect of head position on changes in NC and OC lengths based on the 90th percentile in the two weight groups. In infants weighing less than 1000 g, maximum flexion decreased NC distance by 1.0 cm and OC distance by 1.5 cm, whereas maximum extension increased NC distance by 0.8 cm and OC distance by 1.3 cm. In infants weighing 1000 g or more, maximum flexion decreased NC distance by 1.6 cm and OC distance by 1.0 cm, while maximum extension increased NC distance by 1.7 cm and OC distance by 1.5 cm. The effects of head positioning on NC distance were not statistically different from its effects on OC distance.

In the two infants (26 and 41 weeks of gestation) in whom measurements were taken both in situ and after removal of the trachea at postmortem examination, the VC lengths were longer when measured in situ than after removal of the trachea (3.5 vs 2.8 cm in one infant and 5.0 vs 4.0 cm in the other).

Radiologic Study

Radiologic measurements of NC distances were performed in 40 infants whose corrected gestational ages ranged from 23 to 42 weeks. Population descriptors are given in Table 1. Simple linear regressions of NC distance with CRL, CHL, and OFC each provided highly significant linear relationships ($P < .0001$). The estimated equations obtained from the radiologic study did not differ significantly from those obtained from the postmortem study. Neither the slope ($P = .11$) nor the intercept ($P = .20$) in the relationship between NC distance and CRL differed between these two methods (Fig 3).

COMMENT

Tracheal length is a physiologic and functional dimension that is affected by both respiratory movements¹ and changes in head posture.^{1,10} The trachea lengthens and widens during inspiration and shortens and narrows during expiration.¹⁴ The results of our study concur with those of others^{10-12,15} that significant changes in tracheal length are associated with extension and flexion of the head, while lateral rotation produces minimal changes. Thus, these functional changes must be considered when attempting to define the optimal length of the ETT during intubation.

Discrepancies in tracheal dimension (VC length) reported in different studies are probably related to the limitations of the various methods used. Due to changes in tissue elasticity after death and during preservation, measurements of tissues removed from cadavers^{3,4} may not reflect the true tracheal length in a live infant. Also, direct measurements on excised airways at autopsy^{3,4} may be shorter than normal once tissue attachments are severed. This is suggested by our finding of shorter VC lengths in excised trachea. Conversely, measurements by direct rigid bronchoscopy⁵ may produce longer than normal tracheal lengths due to relative extension of the head during this procedure. Results from radiologic studies^{1,2,7-9}

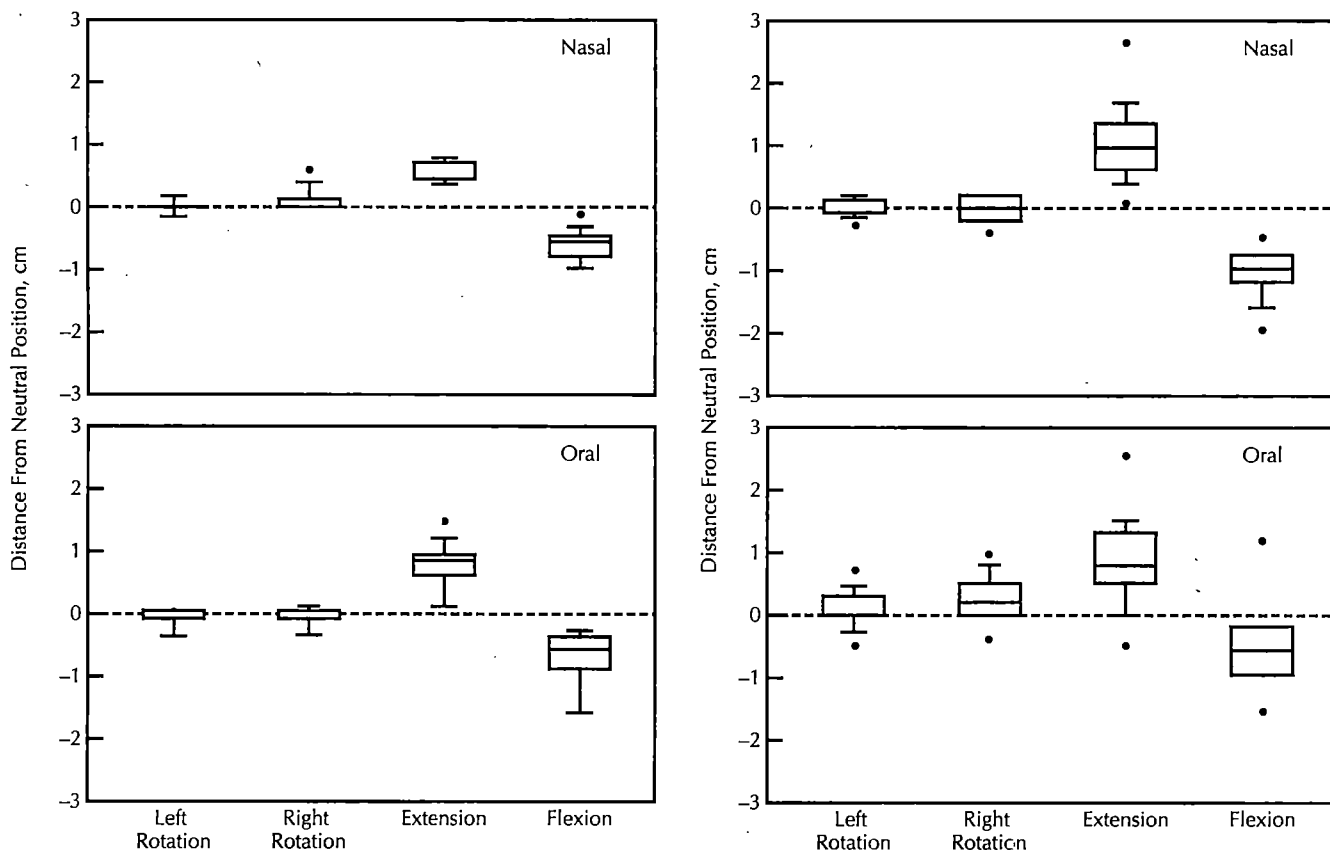


Fig 2.—Changes in nasal-carina and oral-carina lengths with changes in head position in infants weighing less than 1000 g (left) and infants weighing 1000 g or more (right). Data are displayed by box plots. The lower line of the box is the 25th percentile, the midline the 50th percentile (median), and the upper line the 75th percentile. The horizontal bars below and above the hatched boxes represent the 10th and 90th percentiles, respectively. Dots represent measurements beyond the 10th and 90th percentiles. Lines may be missing when values are the same.

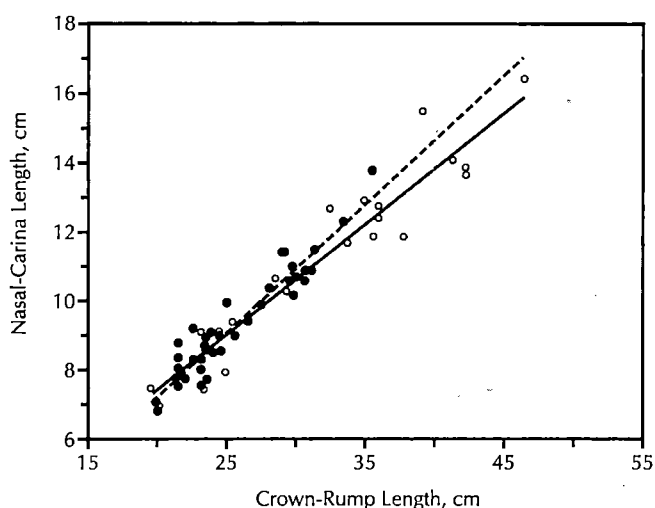


Fig 3.—Relationship between nasal-carina (NC) distance and crown-rump length (CRL) from radiologic (broken line and closed circles) and postmortem (solid line and open circles) data. Regression equations are $NC = 0.52 + 0.33CRL$ (radiologic data) and $NC = 1.52 + 0.29CRL$ (postmortem data). Slopes and intercepts were not significantly different between these two data sources.

may also be affected by several potential sources of error. In the retrospective studies, the position of the infant's head during exposure for the roentgenogram is not

always specified. Studies using the fourth thoracic vertebral body as the radiologic landmark for the carina to measure the ETT tip to carina distance may not be reliable. In the very-low-birth-weight infants, a topographic study¹⁶ has shown that the carina level can be as high as the third thoracic vertebral body during the third trimester of gestation.

Measuring upper-airway dimensions in situ in fresh autopsy specimens avoids some of these sources of error. Moreover, obtaining these measurements with the head in different positions may demonstrate the effect of head movement on the length of the airway.

Although other studies have found linear relationships of upper-airway dimensions to CHL^{7,8} and weight,³ we found that the best correlation of all three dimensions—VC, OC, and NC distances—was with CRL and CHL. The linear relationship of NC distance with CRL, OFC, and CHL from the radiologic study was almost identical to that from the postmortem study, thus confirming that the results from our postmortem study are applicable clinically.

Weight is a routine measurement, but it does not give the best correlation. Of interest, for infants weighing less than 1000 g, the optimum ETT length for nasal intubation varied only from 6.9 to 7.4 cm for weights between 600 and 1000 g (Table 2).

When we looked at the effect of head positioning on

Table 2.—Regression Equations*

Anthropometric Measurements	Regression Equations		
	NC Distance	OC Distance	VC Distance
CRL	$1.659 + 0.285\text{CRL}$ (R^2 -.91)†	$0.933 + 0.261\text{CRL}$ (R^2 -.84)	$0.708 + 0.106\text{CRL}$ (R^2 -.71)
CHL	$0.735 + 0.225\text{CHL}$ (R^2 -.91)	$0.262 + 0.202\text{CHL}$ (R^2 -.81)	$0.423 + 0.082\text{CHL}$ (R^2 -.69)
WT	$7.738 + 0.0014\text{WT}$ (R^2 -.82)	$6.479 + 0.0013\text{WT}$ (R^2 -.76)	$3.005 + 0.0005\text{WT}$ (R^2 -.62)
OFC	$0.437 + 0.332\text{OFC}$ (R^2 -.90)	$0.441 + 0.313\text{OFC}$ (R^2 -.82)	$0.306 + 0.123\text{OFC}$ (R^2 -.62)

*Regression equations were derived from the postmortem anthropometric measurements of each of crown-rump length (CRL), crown-heel length (CHL), weight (WT) and occipitofrontal head circumference (OFC) with each of the upper airway dimensions of nasal-carina (NC), oral-carina (OC), and vocal cord-carina (VC) distances. All lengths and distances are in centimeters, and weights are in grams.

†The quantity R^2 measures the fractions of total variation around the mean explained by the regression equation. In simple regression provides one measure for comparing the quality of the estimation.

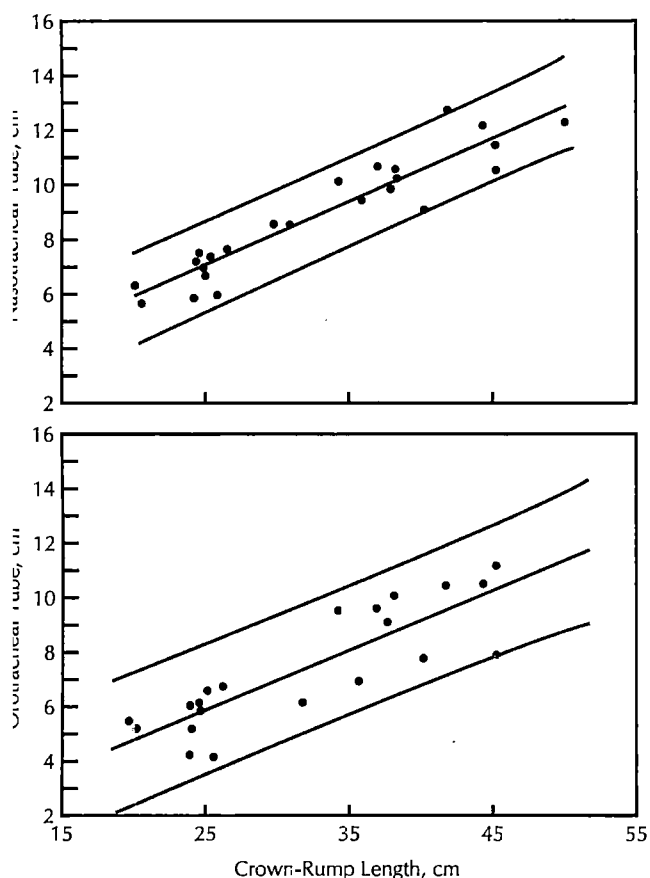


Fig 4.—Graph for prediction of optimal endotracheal tube lengths for nasotracheal and orotracheal intubation based on the external measurement of crown-rump lengths. Center line is the regression estimate; outside curves are 95% prediction intervals, based on SEs of prediction. Some points are obscured because of nearly concurrent values.

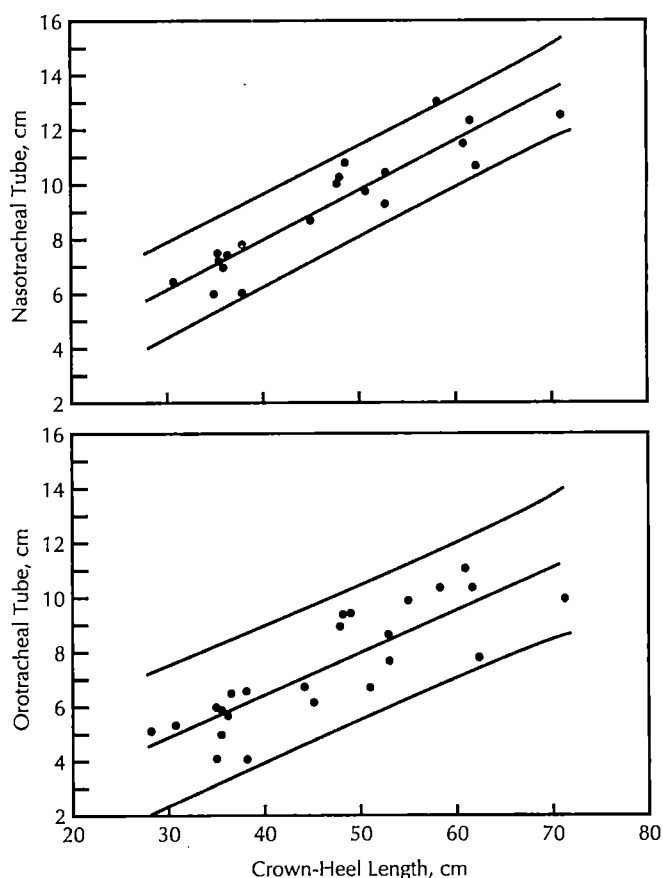


Fig 5.—Graph for prediction of optimal endotracheal tube lengths for nasotracheal and orotracheal intubation based on the external measurement of crown-heel lengths. Center line is the regression estimate; outside curves are 95% prediction intervals, based on SEs of prediction. Some points are obscured because of nearly concurrent values.

Upper-airway measurement, flexion decreased whereas extension increased both the NC and OC lengths. We can deduce that with either nasal or oral intubation, flexion pushes the ETT tip toward the carina and extension retracts the tip away from the carina. This information will

be useful for the nursing care of intubated infants. Based on the 90th percentile of changes in ETT position with maximum flexion and extension, a safe position of the ETT tip for infants weighing less than 1000 g is defined as at least 0.8 cm below the vocal cords and more than 1.0

cm above the carina during nasal intubation, and 1.3 and 1.5 cm, respectively, during oral intubation. The corresponding safe ETT tip position for infants weighing 1000 g or greater should be at least 1.7 cm below the vocal cords and at least 1.6 cm above the carina during nasal intubation, and 1.5 cm below the vocal cords and 1.0 cm above the carina during oral intubation. It can be deduced from these figures that the ideal safe position for the ETT tip with both routes of intubation is the midtracheal position for both groups of infants.

In this study, although maximum flexion and extension of the head produced a wider scatter in OC length changes than NC length changes, there was no statistically significant difference in the changes whether the infant was intubated nasally or orally. This finding contrasted with that of Donn and Blane,¹² who found greater ETT movement with nasotracheal intubation in their postmortem study of a single infant weighing 1100 g at birth.

Based on our findings, we have formulated a method of predicting the optimal ETT lengths from naris or upper lip to midtrachea during nasotracheal and orotracheal intubation based on CRL and CHL. The midtracheal distances were computed by subtracting half the VC distance from the NC and OC distances, respectively. By using linear regression, the linear relationships of the naris to midtrachea and upper lip to midtrachea distances with CRL (Fig 4) and CHL (Fig 5) were obtained. These graphs can serve as initial guidelines for determining the ETT lengths for either nasal or oral intubation using an endotracheal tube marked at centimeter intervals from its tip.

The ETT position can be further confirmed by noting the depth of the ETT tip from the vocal cords during intubation. This should be at least 1.3 to 2.0 cm, depending on the size of the infant. We also recommend that the infant's head be held in the neutral position when localizing of the tip of the ETT is attempted.

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The Causes and Complications of Late Diagnosis of Foreign Body Aspiration in Children: Report of 210 Cases

Liancai Mu, MD; Ping He, MD; Deqiang Sun, MD
(*Arch Otolaryngol Head Neck Surg*. 1991;117:876-879)

Oral Vaccine Therapy for Pneumococcal Otitis Media in an Animal Model

Hiroyuki Yoshimura, MD; Noritake Watanabe, MD;
Junichi Bundo, MD; Mitsunori Shinoda, MD
(*Arch Otolaryngol Head Neck Surg*. 1991;117:889-894)

Evaluation of Auditory Brain-stem Response in Full-term Infants of Cocaine-Abusing Mothers

Ronald P. Carzoli, MD; Suzanne P. Murphy, PhD; Judy Hammer-Knisely, MA, CCC-A; Jean Houy, ARNP

● The purpose of this study was to examine the association between perinatal cocaine exposure and the prevalence of hearing deficit in the newborn. Auditory brain-stem response testing was performed on 50 infants of cocaine-abusing mothers and 50 control infants. All infants were born at full term. Cocaine-exposed infants had lower birth weights and a greater incidence of maternal tobacco and alcohol use. No differences were found in size, method of delivery, Apgar scores, or use of other illicit substances. Four infants of cocaine-abusing mothers and two control infants failed initial auditory brain-stem response testing. There were no differences in absolute or interpeak latencies of waveforms noted between the two groups. These data suggest that there is no increased incidence of hearing deficit as determined by auditory brain-stem response in newborns of cocaine-abusing mothers born at term and without other risk factors.

(AJDC. 1991;145:1013-1016)

Cocaine abuse during pregnancy has increased dramatically in recent years, paralleling the increased use in the general population. Seventeen percent of pregnant women have been estimated to use cocaine at least once during pregnancy.¹ Cocaine is a potent vasoconstrictor that has been shown in animal studies to decrease uterine blood flow, resulting in fetal hypoxemia, hypertension, and tachycardia.^{2,3} In infants of cocaine-abusing mothers (ICAMs), a variety of perinatal and neonatal complications have been reported, including relative or absolute microcephaly and a high prevalence of small-for-gestational-age infants.^{4,7} Neurologic problems include perinatal cerebral infarction, cranial ultrasound abnormalities such as intraventricular hemorrhage, brain necrosis, and cavitory lesions, transient electroencephalographic changes, and retinal and other ocular anomalies.⁸⁻¹¹ In addition, cardiorespiratory pattern ab-

normalities such as increased incidence of periodic breathing and apnea have been reported.¹² Finally, using the Brazelton Neonatal Behavioral Assessment Scale, depression of interactive behavior and poor organizational response to environmental stimuli have been noted.¹³ However, the effect of perinatal cocaine exposure on the auditory system in the neonate has remained largely unexplored, and in view of the aforementioned effects on neurodevelopmental outcome, needs to be examined. The present study was designed to determine whether the prevalence of sensorineural hearing deficit, using the auditory brain-stem response (ABR), is greater in full-term infants exposed to cocaine prenatally than in age-matched control infants of mothers who did not use cocaine.

SUBJECTS AND METHODS

All infants enrolled in the study were born at the University of Florida Health Science Center, Jacksonville, between April 1989 and February 1990, and were admitted directly to the normal newborn nursery. Only apparently healthy, full-term infants, of at least 37 weeks' gestation, were included in the study population. The cocaine-exposed group consisted of ICAMs, as determined either by maternal history of cocaine use during pregnancy or infants in whom maternal cocaine abuse was suspected and results of urine toxicology examination for cocaine metabolites were positive. Infants were routinely screened for urine cocaine metabolites if pregnancy was complicated by a known history of maternal substance abuse, no prenatal care, abruptio placentae, precipitous delivery, home delivery, or the presence of certain congenital malformations.

Infants in the control group were born to women with uncomplicated pregnancy including no maternal history of cocaine use, and had no detectable cocaine metabolites on urine screening. Infants with known or suspected risk factors for hearing loss (family history of hearing impairment before age 6 years; congenital toxoplasmosis, other [syphilis, hepatitis, zoster], rubella, cytomegalovirus, and herpes simplex [TORCHES] infection; sepsis; bilirubin levels of 256.5 $\mu\text{mol/L}$ or more; Apgar scores less than or equal to 6 at 5 minutes; intraventricular hemorrhage; seizures; birth weight less than 1500 g; aminoglycoside use longer than 10 days; craniofacial anomalies; renal malformations; or other congenital malformation) were excluded from the study.^{14,15}

Other information obtained on all infants included birth weight, gestational age, size for gestational age, 1- and 5-minute Apgar scores, and method of delivery. Gestational age was based on maternal dates if within 2 weeks of the Dubowitz score, or otherwise as assessed with the Dubowitz scale.¹⁶ Mothers

Accepted for publication March 21, 1991.

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Table 1.—Frequency Distributions of Background Variables of 50 Cocaine-Exposed and 50 Nonexposed Newborns*

Variable	Cocaine-Exposed Infants, No. (%)	Nonexposed Infants, No. (%)	χ^2	P<
Sex				
M	20 (40)	20 (40)	0	.99
F	30 (60)	30 (60)		
Race				
W	11 (22)	20 (40)	3.79	.10
B	39 (78)	30 (60)		
Size				
SGA	11 (22)	3 (6)	5.69	.10
AGA	37 (74)	43 (86)		
LGA	2 (4)	4 (8)		
Delivery				
Vaginal	44 (88)	41 (82)	0.71	.50
C-Section	6 (12)	9 (18)		
Maternal substance use				
Tobacco	38 (76)	14 (28)	23.08	.001
Alcohol	17 (34)	6 (12)	6.83	.01
Marijuana	6 (12)	3 (6)	1.10	.30

*SGA indicates small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; and C-section, cesarean section.

were questioned as to their use of tobacco, alcohol, marijuana, and other illicit drugs during pregnancy. Cocaine use was divided into first, second, and/or third trimester usage.

Cocaine urine screening was performed in all infants with a cocaine metabolite assay (ADx, Abbott Laboratories, Abbott Park, Ill), and was considered positive when 0.3 $\mu\text{g}/\text{dL}$ or more was detectable.

Hearing was screened in all infants within the first week of life using the ABR. Infants who failed initial ABR testing were scheduled for repeated ABR testing after postconceptual age 44 weeks, because thresholds do not change significantly after this age.¹⁷ The sensitivity of the ABR test has been predicted to be as high as 100%, and specificity, 86%. The predictive value of a positive test is 5.3% and of a negative test is 100% in a high-risk population.¹⁸ Although the ABR test is not considered a definitive predictor of hearing loss later in life, it is currently considered the most reliable instrument for assessing the integrity of the auditory system in infancy.^{19,20}

The test was administered by a certified audiologist who was blinded to the infant's group. Testing was done using an auditory evoked potential electrodiagnostic computer and averaging system (Nicolet Compact Four, Nicolet Biomedical Instruments, Madison, Wis). Electrode placement consisted of three silver 6-mm cup electrodes. Placement of the active (noninverting) electrode was at the forehead, with the reference (inverting) electrode attached to the earlobe of the test ear and the ground electrode attached to the contralateral earlobe. Click stimuli were presented to each ear separately at a repetition rate of 21.1 clicks per second through tubal insert phones and immittance tip adaptors at an intensity level of 30 dB relative to normal hearing threshold (dBnHL). To obtain a quiet recording, filters were used to eliminate background electroencephalographic noise below 150 Hz and above 3000 Hz. Recordings were obtained by averaging 2000 stimulus presentations, with reproducible waveforms obtained in at least two separate trials. All testing was performed in a sound-treated chamber (model RS 2425, Acoustic Systems, Austin, Tex).

Table 2.—Comparison of Background Characteristics Between Cocaine-Exposed and Nonexposed Infants*

Variable	Values		
	Mean (SD)	Median	Range
Gestational age, wk			
Cocaine-exposed	39.36 (1.22)	40	37-42
Nonexposed	39.10 (1.03)	39	37-42
Birth weight, g			
Cocaine-exposed	2844 (465.99)	2745	2015-3884
Nonexposed	3140 (428.32)	3230	2065-4040
Apgar score			
1 minute			
Cocaine-exposed	7.80 (1.27)	8	4-9
Nonexposed	7.84 (1.60)	8	1-9
5 minutes			
Cocaine-exposed	8.94 (0.47)	9	7-10
Nonexposed	8.98 (0.47)	9	7-10

*The results of independent *t* tests indicated a significant difference between cocaine-exposed and nonexposed infants for birth weight ($P \leq .001$), but not for gestational age ($P \leq .25$), 1-minute Apgar score ($P \leq .88$), or 5-minute Apgar score ($P \leq .66$).

Table 3.—Frequency of Maternal Cocaine Use by Trimesters

Trimester	No. Admitted Use	Positive Urine Screen	Adjusted Usage*
1 only	12	3	9
2 only	2	1	1
3 only	2	2	2
1 and 2	8	5	3
2 and 3	1	1	1
1, 2, and 3	22	18	34
Denied use	...	3	...

*Adjusted use indicates that any mother who denied use during the third trimester, but had an infant whose urine sample showed positive results, was presumed to have used cocaine during all three trimesters. This included a total of 12 women, three of whom denied cocaine use at any time during pregnancy.

Hearing evaluations were scored on a pass/fail basis. Infants were considered to have passed the ABR test if waves I, III, and V were present at 30 dBnHL with good wave reproducibility, interaural agreement, and morphologic features. Latencies of waves were recorded at 30 dBnHL for comparison between study and control groups. In infants who failed the initial ABR, follow-up testing included latency intensity function and immittance, in an attempt to distinguish conductive from sensorineural hearing loss.

RESULTS

Consents were obtained for a total of 112 infants, but 12 were excluded due to incomplete data, other risk factors for hearing impairment, or ABR test not being performed within the first week of life. Therefore, a total of 50 ICAMs and 50 control infants were enrolled in the study and underwent ABR examinations.

Urine samples of all infants were screened for cocaine

metabolites within the first 48 hours after delivery. Results of urine toxicologic tests were positive (greater than 0.3 µg/dL) in 33 of the 50 infants in the cocaine-exposed group. No control infants had detectable cocaine metabolites on urine screening.

In the cocaine-exposed newborns, 46 passed the initial ABR test and four failed, compared with 48 passes and two failures in the control group. Using χ^2 analysis with Yates' correction for continuity, this difference was not significant ($\chi^2=0.18$ [$df=1$]). Using one-tailed independent t tests, no significant differences were noted between the two groups in absolute latencies of waves I, III, and V or III to V and I to V interpeak latencies for either the left or right ear.

Background characteristics of infants in the two groups are presented in Tables 1 and 2. Cocaine-exposed infants had a lower mean birth weight ($P<.001$) and a higher incidence of maternal use of tobacco ($P<.001$) and alcohol ($P<.01$). There were no significant differences found in mode of delivery, 1- or 5-minute Apgar scores, or use of other illicit substances.

Table 3 depicts the estimated pattern of maternal cocaine use by trimester. Adjusted use in pregnancy was greater than admitted use, based on the number of positive infant urine screens. A total of 12 women denied third trimester cocaine use, yet cocaine metabolites were found in their infants' urine samples. These women were considered to have used cocaine during all three trimesters, as historical information obtained was considered unreliable.

In all, at least 46 women used cocaine during the first trimester, 39 were second trimester users, and 37 women used cocaine during the last trimester of pregnancy. According to adjusted usage rates, the majority of women who used cocaine did so throughout pregnancy. The second largest group comprised first trimester users only. Based on histories obtained from these women in the latter group, most indicated attempting to stop cocaine use once they discovered they were pregnant, due to concerns of effects on the developing fetus. Several of the women had voluntarily entered treatment programs in an attempt to overcome their addiction.

Of the six infants who failed initial ABR testing, all were appropriate for gestational age in size. Five of six mothers whose infants failed initial ABR testing used tobacco during their pregnancy. Results of repeated ABR tests were normal in five of the six infants. The only infant who failed follow-up testing had latency intensity curves and admittance measurements indicative of a conductive rather than sensorineural hearing loss. This infant had a history of recurrent otitis media, and was referred for further evaluation.

COMMENT

Based on previously published reports on neurodevelopmental problems in ICAMs, abnormalities on infant hearing evaluation by ABR testing were expected, but no such abnormalities were found. In this study, no significant increase in sensorineural hearing loss was observed in ICAMs compared with control infants. The relatively high false-positive rate on initial testing found in this study has also been reported by others.^{18,21} The one infant who did fail repeated ABR testing was diagnosed to have conductive rather than sensorineural hearing loss, which was presumed secondary to recurrent otitis media

and not due to perinatal cocaine exposure. Although no differences between the two groups were noted, further study with larger samples will be needed to confirm these results. Confirmed hearing loss in high-risk populations, most notably infants in neonatal intensive care units with various risk factors, has been estimated at between 2% and 4% and higher.^{18,21} The estimated incidence of hearing loss in the general population is approximately one in 750 infants.¹⁵

These findings are in contrast to a previously published report by Shih et al,²² which indicated prolonged interpeak and absolute latencies in 18 ICAMs compared with 18 control infants. However, the increase in absolute latencies reported in the study by Shih et al occurred only at high intensities (80 dBnHL) and only for wave V. Prolonged interpeak latencies were seen at 40 and 80 dBnHL for the wave III to V interval, and for the wave I to V interval at 80 dBnHL, indicating possible slower brain-stem transmission times at higher intensities. Higher stimulus rates were used (60 per second), and the latency prolongation seen may indicate prolonged brain-stem neuronal refractory periods in cocaine-exposed infants. However, their population of cocaine-exposed infants had gestational ages ranging from 32 to 40 weeks. It has been shown that there is a progressive neuromaturational decrease in wave latencies and hearing threshold with increasing gestational age.^{17,23,24} Therefore, the latencies reported by Shih et al may have been prolonged as a result of the pre-term infants, thus biasing the results, although it may indicate subtle auditory brain-stem dysfunction at higher stimulation rates.

Compared with the control group, the ICAM population in the present study was found to have significantly lower birth weights, as has been reported by others,^{4,7,13} although no cause-and-effect relationship can be proposed. A variety of other factors may influence the intrauterine growth of ICAMs, including maternal smoking and nutritional and socioeconomic status. Mothers who used cocaine during the pregnancy were also more likely to use tobacco and alcohol, although there was no reported difference in other illicit drug use. There was also no difference in Apgar scores at 1 and 5 minutes or method of delivery between the two groups. The lack of difference in size between infants who were exposed to cocaine and those who were not may be partly explained by the fact that only apparently healthy infants of over 37 weeks' gestation were chosen for the study.

Therefore, despite numerous other neurologic complications reported in ICAMs,^{4,13} the present results suggest that there was no apparent effect on the developing auditory system in otherwise healthy, full-term infants due to maternal cocaine abuse. It remains to be seen whether infants born prematurely or with congenital abnormalities directly attributable to maternal cocaine use will be similarly unaffected.

This study was supported by a grant from the Department of Sponsored Research, University of Florida, Gainesville.

We are grateful to Kathy Beaulieu and Karen Richard for their help in preparation of this article.

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Persistent Hyperplastic Primary Vitreous With Glaucoma Presenting in Infancy

Wallace L. M. Alward, MD; Michael A. Krasnow, DO;
Ronald V. Keech, MD; Jose S. Pulido, MD; Gregory L. Sutton, MD
(*Arch Ophthalmol.* 1991;109:1063-1066)

Ductal Patency in Neonates With Respiratory Distress Syndrome

A Randomized Surfactant Trial

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• The purpose of this study was to evaluate in a controlled study the effect of exogenous surfactant on various manifestations of ductal patency. Premature infants with respiratory distress syndrome were randomized to receive surfactant (Survanta) (n=22) or air (n=14). In neonates receiving surfactant, there was a greater tendency for an audible murmur to develop (13 of 22 vs four of 14). In spite of this, the clinical use of indomethacin was similar for the two groups, 10 (45%) of 22 vs six (43%) of 14. Excluding neonates given indomethacin early, a comparable number of surfactant-treated neonates (9/17 [53%]) vs control neonates (6/12 [50%]) demonstrated spontaneous closure of the ductus within a physiologic time frame (on or before day 4). For the gestational ages studied, the beneficial effects of exogenous surfactant were not associated with either an increased risk for delayed closure of the ductus arteriosus or a greater incidence of indomethacin usage. Utilization of exogenous surfactant does not appear to have an adverse impact on ductal patency.

(AJDC. 1991;145:1017-1020)

Premature neonates with respiratory distress syndrome are at well-recognized risk for persistent shunting through the ductus arteriosus. Currently, the treatment of premature neonates frequently includes the use of exogenous surfactant to reduce the severity and complications of respiratory distress syndrome.¹⁻⁶ However, little objective information exists regarding the effect of surfactant administration on ductal patency. Symptoms of ductal shunting have been reported to be more frequent after surfactant treatment,¹ and concerns exist that this shunting could either affect the resolution of respiratory distress¹ or be associated with a transient or poor response to surfactant.⁷ Additionally, surfactant therapy has been

reported to be associated with a greater need to treat symptomatic patent ductus arteriosus.⁸ While several other investigational trials have not reported an increased incidence of clinically significant patent ductus arteriosus,^{4,9-13} the assessment of ductal patency was not the primary focus in any of these studies. Additionally, because no uniform or objective criteria exist for determining significant ductal shunting, the "incidence" of patent ductus in most of these randomized trials has depended on a variety of clinical and/or subjective echocardiographic criteria.

In previous studies evaluating ductal patency,^{14,15} we have utilized duration of ductal patency (ie, timing of functional closure) as one objective end point and have established normative data for the timing of spontaneous ductal closure in premature neonates.¹⁴ The purpose of the current study was to systematically evaluate the impact of surfactant, administered in a randomized prospective trial, as to its impact on the timing of spontaneous ductal closure. Because indomethacin sodium trihydrate administration obviously affects the timing of ductal closure, we specifically analyzed a subgroup of neonates who did not receive indomethacin during the first 4 days of life (the normal time frame of physiologic ductal patency) as to the risk factors associated with delayed ductal closure. We separately analyzed two clinical manifestations of ductal patency: the need for indomethacin (as clinically determined by the neonatal attending staff), and the incidence of cardiac murmurs in neonates with ductal patency confirmed by echocardiography.

PATIENTS AND METHODS

Thirty-seven neonates were enrolled into this investigation over a 19-month period between March 31, 1988 and October 15, 1989. Of these, 28 neonates were delivered at the Oregon Health Sciences University Hospital, Portland, while nine were outborn referrals. Criteria for inclusion into this study were (1) birth weight below 1750 g; (2) gestational age greater than 26 weeks (confirmed by a neonatal modified Ballard examination); (3) positive-pressure ventilatory support with fraction of inspired oxygen (Fio₂) of 0.40 or greater (with Pao₂ ≤80 mm Hg); (4) absence of congenital malformation; and (5) signed parental consent.

Accepted for publication March 28, 1991.

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Presented before the Society for Pediatric Research, Anaheim, Calif, May 10, 1990.

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Table 1.—Factors Associated With Delayed Closure of the Ductus Arteriosus*

	Normal Closure (n = 15)	Delayed Closure (n = 14)
Birth weight, g	1355 ± 304	1286 ± 258
Gestational age, wk	29.8 ± 1.2	28.7 ± 1.6†
Apgar score		
1 min	5.9 ± 1.8	3.4 ± 2.3‡
5 min	7.4 ± 1.3	5.6 ± 2.3†
Positive pressure ventilation (day 4)	6 (40)	11 (79)†
Exogenous surfactant	9 (60)	8 (57)

*Data for the subgroup of infants who did not receive indomethacin in the first 4 days of life. Values are mean ± SD or number (percent).

† $P < .05$.

‡ $P < .01$.

All neonates entered into this study had previously been enrolled in a prospective, randomized, blinded trial to assess the effects of surfactant administration in premature neonates with respiratory distress syndrome and assisted positive-pressure ventilation (for which a separate signed consent was obtained). The surfactant preparation used in this study was an organic solvent extract of minced cow lung supplemented with dipalmitoyl phosphatidylcholine, palmitic acid, and tripalmitin (Survanta, Ross Laboratories, Division of Abbott Laboratories, Columbus, Ohio). The initial dose was administered between 1 and 8 hours of life. The dose of surfactant was 100 mg/kg (4 mL/kg). Control neonates were administered air. Subsequent doses up to a total of four could be given in the first 48 hours of life if continued ventilatory support and F_{iO_2} above 0.30 were required. The minimum dose interval was 6 hours.

Neonates enrolled into this investigation were treated by the neonatal attending staff. When criteria for surfactant dosing were met, the surfactant was administered by a separate group of workers not directly involved with care of the neonate. Thus, both the attending staff and our investigational group were "blinded" as to the medication given to the neonates enrolled into the study.

After initiation of the investigational protocol and administration of the first dose of surfactant (or air), a complete two-dimensional echocardiographic study was performed. The initial study was performed in the first 16 hours of life. All subsequent studies were limited to high parasternal and suprasternal notch imaging to optimize visualization of the ductus arteriosus.

For detection of left-to-right ductal shunt flow, color flow Doppler imaging was utilized. With this extremely sensitive tool, ductal flow is noted to originate near the orifice of the left pulmonary artery and generally produces a mosaic pattern. With use of current color flow Doppler imaging techniques, the detection and confirmation of even small left-to-right ductal jets are easily obtained.¹⁴⁻¹⁸

The echocardiograms were obtained using an ultrasound imaging system (Hewlett-Packard Color Flow Ultrasound imaging system, model HP77020A, Hewlett-Packard Co, Andover, Mass). The two-dimensional images and color flow signals were obtained with a 5-MHz short-focus transducer. The two-dimensional and color flow Doppler images were recorded on a videocassette recorder (Panasonic).

For all neonates, daily sequential ductal shunt flow studies were obtained at roughly 24-hour intervals until no shunt flow could be detected on two consecutive studies, signifying that functional closure of the ductus arteriosus had occurred. Functional closure was defined as occurring on the first day that no shunt flow was detected. Studies were also continued following indomethacin administration or ligation until closure of the ductus was confirmed.

A daily cardiac examination was made by a member of our investigational group. This person was blinded to both the medication given as well as the results of the daily echocardiographic evaluation. By design, it was the goal of this study not to alter standard care in the neonatal unit. Thus, to avoid introduction of bias, the results of our daily investigational echocardiograms were not made available to the neonatal staff. In addition, no set criteria were established for the utilization of indomethacin. The decision to administer indomethacin was made solely by the attending neonatal staff. Clinical concerns suggesting significant ductal shunting (ie, new onset murmur, worsening chest roentgenogram, deterioration in ventilatory requirements) usually resulted in cardiology consultation for the assessment of ductal status. As it is not standard practice in our nursery, no neonate received prophylactic indomethacin.

Intravenous fluid administration was not prospectively controlled in this study. However, all neonates were treated using a standard fluid management of 80 mL/kg for 2 days, then 100 mL/kg increasing to 120 mL/kg by day 5. Daily weights were subsequently evaluated.

Statistical differences between the two groups were analyzed using Student's *t* test or by the Mann-Whitney *U* test.

RESULTS

The mean birth weight and gestational ages for the 22 surfactant-treated neonates and 15 control neonates were 1344 ± 291 vs 1270 ± 313 g and 29.3 ± 1.7 vs 29.0 ± 1.5 weeks, respectively (not significant). One of the control neonates died at 20 hours of life and was eliminated from the study. Both groups were maintained in a negative fluid balance and demonstrated comparable weight losses. By day 4, surfactant-treated neonates weighed 8.2% ± 4.5% less than birth weight, compared with 9.2% ± 7.1% less for control neonates.

The echocardiographic evaluations for the two groups of neonates were performed at comparable times. The average age for the two groups on the first 5 days of life for surfactant-treated and control neonates were 10.4 vs 10.3 hours, 33.0 vs 32.8 hours, 57.9 vs 58.0 hours, 83.0 vs 83.0 hours, and 107.1 vs 106.6 hours, respectively.

Healthy premature neonates without respiratory distress undergo spontaneous closure of the ductus arteriosus in the first 4 days of life.¹⁴ To examine the extent to which respiratory distress syndrome and exogenous surfactant affect the timing of ductal closure, we excluded neonates who received indomethacin during the first 4 days of life (five surfactant-treated, two control). Of the 17 surfactant-treated neonates not receiving indomethacin early in life, nine (53%) demonstrated evidence for spontaneous ductal closure by the fourth day of life. For the 12 control neonates not receiving indomethacin early in life, the ductus in six (50%) closed spontaneously by the fourth day of life. For the eight surfactant-treated neonates whose ductus did not close by the fourth day, the ductus in three subsequently closed spontaneously on days 8, 10, and 11, while the other five required either indomethacin or ligation for closure. For the remaining six control neonates, the ductus in two also closed spontaneously on days 5 and 9, while four neonates required indomethacin or ligation for closure. For both groups of neonates, ductal closure occurred within 1 to 3 days of initiation of indomethacin treatment. Thus, surfactant did not appear to alter either the response to indomethacin or the need for ligation.

Approximately 50% of the neonates not receiving indomethacin early in life had delayed closure of the ductus arteriosus (ie, persistent patency). Of the 29 neonates

Table 2.—Ventilator Settings (Day 4) for Infants With Delayed Closure of Ductus Arteriosus and Continued Need for Positive-Pressure Ventilatory Assistance.*

	Surfactant (n = 5)	Control (n = 6)
Peak inspiratory pressure, cm H ₂ O	15.2 ± 4.7	24.0 ± 7.4
Respiratory rate/min	17.8 ± 11.6	37.2 ± 16.4

*Three of the 14 infants with delayed closure from Table 1 were extubated (all received exogenous surfactant). For both variables, $P < .05$.

(from both treatment groups), 15 (nine surfactant-treated, six control) demonstrated ductal closure within the physiologic time frame, while 14 (eight surfactant-treated, six control) did not (Table 1). Delayed ductal closure was associated with lesser gestational age, lower Apgar scores, and continued need for positive-pressure ventilatory therapy.

In this study, two clinical manifestations of ductal patency were evaluated: the presence of a murmur and the need for indomethacin. Of the 22 neonates who received surfactant, 13 had a detectable cardiac murmur coinciding with confirmed ductal patency by echocardiography. Only four of 14 control neonates had a detectable murmur ($P = .07$). The decision to give indomethacin was determined independently by the neonatal attending staff. Of the 22 neonates receiving surfactant, a total of 10 (45%) required indomethacin, three of whom subsequently required ligation of the ductus arteriosus. Of the 14 control neonates, six (43%) received indomethacin with one subsequent ligation. Thus, the clinically determined need for indomethacin was comparable for the two groups.

While it was not the purpose of this study to evaluate the ventilatory effects of exogenous surfactant, the concurrent ventilator settings were noted at the time of our daily echocardiographic studies. Our initial echocardiographic evaluation always followed the first randomized administration of surfactant (or air). At the time of this study (mean, 10.4 hours), the oxygen requirements were significantly lower for the surfactant-treated neonates (FiO_2 , 0.42 ± 0.22 vs 0.70 ± 0.21 ; $P < .01$). This finding persisted on the day 2 study (at about 33 hours) (FiO_2 , 0.36 ± 0.18 vs 0.77 ± 0.23 ; $P < .01$). In addition, at the time of the day 2 study, neonates receiving surfactant required a lower peak inspiratory pressure (15.9 ± 3.1 vs 22.9 ± 6.2 cm H₂O; $P < .01$). This finding persisted even in the subgroup with delayed closure of the ductus arteriosus (Table 2). Last, neonates receiving surfactant were extubated from positive-pressure ventilatory assistance more rapidly. The median duration of ventilatory therapy was through the third day for surfactant-treated neonates (range, 1 to 32 days) vs 8 days for control neonates (range, 1 to 26 days) ($P = .023$). By the fourth day of life, 11 (50%) of 22 surfactant-treated neonates were extubated, while only two (14%) of 14 control neonates were extubated ($P < .05$).

COMMENT

The purpose of this study was to assess the effect of exogenous surfactant on several well-defined manifestations of ductal patency, and to evaluate the risk factors associated with delayed closure of the ductus arteriosus. The primary limitation of this and all studies evaluating

ductal patency is the difficulty in defining clinically significant ductal shunting. Unfortunately, no reliable criteria exist with which to make this determination. Left-sided cardiac dimension measurements (left ventricular dimensions, left atrial-aortic root ratios) are known to be insensitive.¹⁹ On the other hand, simple echocardiographic detection of ductal patency in the first days of life fails to differentiate between pathologic (significant) ductal shunting and physiologic patency before normal closure. We have previously established normative data for the timing of spontaneous ductal closure in healthy premature neonates and have utilized delayed closure as an objective end point that is readily evaluable. Using this end point in the current study, the risk factors associated with persistent ductal patency were lower gestational age, lower Apgar scores, and continued positive-pressure ventilatory assistance, while exogenous surfactant was not associated with delayed ductal closure.

In a previous study, we found a relatively low incidence of persistent patency in premature neonates with respiratory distress syndrome.¹⁵ In that study, however, we only evaluated neonates greater than or equal to 30 weeks gestational age and excluded neonates with low Apgar scores (ie, birth asphyxia). In the current study, the higher incidence of delayed closure would appear to be due to inclusion of neonates both sicker (ie, lower Apgar scores) and gestationally less mature, all of whom required ventilatory assistance. That these were the specific risk factors associated with delayed ductal closure in this study confirms this impression. In evaluating the overall group, approximately 50% demonstrated spontaneous closure of the ductus within the physiologic time frame.

Animal models have suggested that exogenous surfactant might lower pulmonary vascular resistance.^{20,21} Thus, it is possible that although ductal closure rates were comparable, the volume of ductal shunting could be greater in those neonates who received surfactant. Evidence that this was not the case is indirect. First, because the attending staff was blinded as to which patients received surfactant as well as to the results of the daily investigational echocardiograms, the decision to give indomethacin was made independently, usually in conjunction with cardiology consultation. That the utilization of indomethacin was nearly identical would argue against clinically significant differences in ductal shunting. In addition, the reductions in both initial oxygen requirements and peak inspiratory pressure, in conjunction with earlier extubation, argue against the development of greater left-to-right ductal shunts in those neonates who received surfactant. Last, this reduction in ventilatory support with surfactant was present even in the subgroup with persistent ductal patency (Table 2). If differences in ductal shunting existed in neonates receiving surfactant, the shunt volume was not sufficiently large to blunt these beneficial ventilatory effects.

Our conclusion that surfactant does not have an adverse impact on ductal patency differs from that of Charon and colleagues,⁷ who found surfactant-receiving neonates to have a higher incidence of patent ductus arteriosus. In their study, patent ductus arteriosus was diagnosed using only clinical signs, including the presence of a systolic or continuous murmur. Neonates receiving surfactant in our study had a similar tendency for a murmur to develop. Our results also differ from a recent publication by Heldt and coworkers,⁸ who reported an increased incidence of

patent ductus. Their study differed from ours, however, in that their surfactant-treated group included both a prophylactically treated group and a later "rescue" group that experienced mechanical ventilatory assistance and clinical deterioration. This latter group introduced a selection bias not present in their control group. Their study also included a smaller (450 to 1580 g) and gestationally less mature (24 to 29 weeks) group of neonates than included in our study. However, similar to the study of Heldt and coworkers, surfactant utilization was not found to alter either the ductal response to indomethacin or the subsequent need for ligation.

We conclude that the beneficial effects of surfactant administration on oxygenation and duration of ventilatory therapy are not associated with either a greater need for indomethacin or any increased risk for delayed closure of the ductus arteriosus. For the gestational ages studied, while the standard risk factors for delayed ductal closure were confirmed, surfactant does not appear to have had an adverse impact on ductal patency.

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INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on PediaProfen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSEAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

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Safety of a Preadolescent Basketball Program

Margaret E. Gutgesell, MD, MPH

• A preadolescent youth basketball program was prospectively studied to determine injury rates and the kinds of injuries sustained. The overall injury rate was 7.6% (39 injuries among the 510 children aged 5 to 12 years). Girls had a higher injury rate than boys ($P < .02$). Only 12 children (2.4%) suffered significant injuries as defined by the inability to play for at least one session. Most injuries were contusions (35.9%), followed by strains or sprains (28.2%), epistaxis (12.8%), lacerations (5.1%), and one finger fracture (2.6%), the most significant injury. Games were more likely to produce injuries than practice sessions; most injuries occurred in the second half of game play. This study documents a low injury rate in an organized preadolescent basketball program.

(AJDC. 1991;145:1023-1025)

Organized athletics for preadolescent children are an established fact in the United States. The American Academy of Pediatrics' committees on Sports Medicine and School Health have endorsed such programs if appropriate safeguards are followed.¹ Many communities have well-organized basketball programs for this age group. Although injury rates of athletes participating in high school basketball programs have been reported,²⁻⁷ little is known about injury rates in preadolescent basketball programs. A local YMCA youth basketball program with multiple levels of organized play for preadolescents was prospectively studied for one season to determine acute traumatic injury rates and kinds of injuries sustained.

SUBJECTS AND METHODS

The Charlottesville-Albemarle (Va) YMCA youth basketball program has three preadolescent play levels: introductory, grades kindergarten through second (aged 5 to 8 years); grades third through fourth (aged 8 to 10 years); and grades fifth through sixth (aged 10 to 12 years). Each level was divided into teams composed of six to eight children with at least one coach, frequently a parent or a college student. The youngest group of children had eight 1-hour sessions, with each child participating for the full hour. The middle-level youths had 10 1-hour practice sessions and either seven or eight games. Each child played for at least 30 minutes per game. The oldest group had 11 1-hour practice sessions and eight or nine games, with each child playing for at least 30 minutes per game. Mean minimum participa-

tion time for the entire group of children was 1.27 h/wk. Participation time was the same for boys and girls. Because of limited YMCA facilities, all practice sessions and games were held in Albemarle County elementary and junior high schools.

Age, sex, school level, telephone number, team, and coach's name and telephone number were available for all children through registration. Coaches were asked to complete a practice/game report for each week of the season with regard to injury occurrence. For this study, an injury was defined as an acute traumatic event occurring during a practice or game that caused the youth to miss the remaining time in practice or in the game or required the youth to have first aid administered or seek an injury assessment before returning to play. If no injuries occurred, the coach stated such.

If an injury did occur, the coach listed the child's name, how the injury happened, the nature of the injury, and any first aid administered. The coach also noted if the injury had occurred in a practice or a game and, if in a game, in which quarter. For those children listed, the parent was contacted to confirm the injury and to obtain other information, such as exact nature of injury, necessity of a physician visit, and missed school and/or practice or games. If a team's weekly game report was not turned in, the coach was contacted by telephone. Confirmatory evidence of fracture was obtained through the child's physician. This project was approved by the Human Investigation Committee of the University of Virginia Health Sciences Center.

RESULTS

The overall injury rate was 7.6% (39 injuries among the 510 children participating in the 1989-1990 season). Girls

Department Editors.—William B. Strong, MD, Augusta, Ga; Carl L. Stanitski, MD, Pittsburgh, Pa; Ronald E. Smith, PhD, Seattle, Wash; Jack H. Wilmore, PhD, Austin, Tex

Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editor's Comment.—Physical education, unfortunately, is being reduced in many schools. Community recreation programs are becoming the major source of physical activity for many children. A knowledge of the expected injury rates and their epidemiology will be useful in reducing their incidence. This is the second study to demonstrate greater injury rates in girls than in boys. This suggests that more attention to the development of the proper motor skills and to conditioning could eliminate some of the injuries.—W.B.S.

Accepted for publication May 3, 1991.

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Reprints not available.

Table 1.—Injury Rates in a Preadolescent Basketball Program

Grade	No. of Participants, M/F	Total
K-2	105/14	119
3-4	143/41	184
5-6	158/49	207
Total	406/104	510

	No. (%) of Injuries, M/F	Total No. (%) of Injuries
K-2	0	0
3-4	15 (10.5)/8 (19.5)	23 (12.5)
5-6	10 (6.3)/6 (12.2)	16 (7.7)
Total	25 (6.2)/14 (13.5)*	39 (7.6)

* $\chi^2=6.131$; $P<.02$.

Table 2.—Types of Injuries Among 510 Children in a Preadolescent Basketball Program

Injury	No. (%) of Cases
Contusion	14 (35.9)
Strain/sprain	11 (28.2)
Epistaxis	5 (12.8)
Laceration	2 (5.1)
Finger fracture	1 (2.6)
Miscellaneous	6 (15.4)
Total	39 (100)

had a higher injury rate than boys (14 of 104 [13.5%] vs 25 of 406 [6.2%]; $\chi^2=6.131$, $P<.02$) (Table 1). None of the introductory-group children sustained injuries in the eight hours of play.

Most injuries (35 of 39 [90%]) occurred in games rather than in practice, and in those injury reports indicating the quarter in which injury occurred, most (19 of 27 [70.4%]) occurred in the second half. Fourth-quarter injuries accounted for 40.7% of all injuries.

The types of injuries are shown in Table 2. The most common type was contusion (35.9%). Strains and sprains accounted for 28.2% of injuries. There were five finger injuries, four finger "jams," and one fracture of a fifth finger near the distal interphalangeal joint. A finger "jam" is a mild sprain of the proximal interphalangeal joint. The five episodes of epistaxis occurred in the third through fourth-grade group. These were all secondary to direct trauma. Miscellaneous injuries included minor eye trauma and a swollen lip. Lower extremity trauma accounted for 14 injuries, half of which were to the knee. There were two knee injuries listed as sprains or strains and five contusions. There were four ankle injuries.

First aid, most commonly application of an ice pack, was administered in 22 of the 39 cases of injury. Ten children sustained injuries that required them to sit out the remainder of the game/practice session. Additionally, two children sustained injuries, returned to the game/practice session, but missed two subsequent sessions (one practice session and one game each) because of their injuries. Only five injuries prompted physician assessment, including the finger

fracture. This injury, in a 10-year-old boy, necessitated a visit to a hospital emergency department, roentgenography, splinting, a follow-up physician visit, and a second roentgenogram. The child missed 3 weeks (six sessions) of play. Only one of the other four children with physician-assessed injuries missed playing time (one session).

If missed playing time is used as the definition of a significant injury, the overall injury rate was only 2.4% (12 of 510). Boys had eight of these injuries. Although most injuries (36 of 39) occurred on a linoleum-tile playing surface, not in a standard wood-floor gymnasium, this was not out of proportion with the number of players participating in games played on linoleum (453 of 510 children [89%]).

COMMENT

The rates of injury in this preadolescent population are much lower than those reported among high school athletes participating in basketball and soccer, both limited-contact sports. McLain and Reynolds⁶ reported injury rates of 37% for boys and 31% for girls, defining an injury as an incident resulting from athletic participation that kept an athlete from completing a practice or game or that caused the athlete to miss a subsequent practice or game. Powell⁷ reported that approximately 22% of both boys and girls playing high school basketball sustained at least one time-loss injury per year. However, Austin and colleagues⁴ noted only 3.6 injuries per 100 participants in twice-weekly high school physical education classes. In a study of soccer injuries in youths ages 6 to 17 years, Backous et al⁸ compared injury rates by age group and found that older youths had higher injury rates than did younger ones in a one-week soccer camp. They believed more aggressive play and greater risk-taking contributed to the older soccer athletes' higher injury rate. The low injury rates in this study are probably related to the total amount of time spent in practice and game sessions. Although the study design did not allow the detection of overuse injuries, it is unlikely that they would have occurred because of the limited playing time.

The data in this report might underestimate the total number of injuries if a coach did not document all injuries. Using the missed time and/or first aid requirement as an injury definition should have eliminated underreporting of injuries. If anything, the coaches probably overreported injuries.

Although girls had a higher overall injury rate, their rate of significant injury was similar to that of boys. This is in contrast to data from McLain and Reynolds' study,⁶ in which girls had fewer but more severe injuries. Their data were skewed by one girl who was out of play for 300 days due to an anterior cruciate ligament tear. It is not clear why girls in our study had a higher injury rate.

The fact that more injuries occurred in games rather than in practice is not surprising owing to the competitive nature of a game. Increased frequency of injuries in the second half has also been reported.⁷ This may be related to the young athlete becoming tired near the end of the game.

The types of acute traumatic injuries sustained by this group of young athletes were similar to those described by McLain and Reynolds,⁶ even in the absence of an athletic trainer in our study. Because of the nature of basketball, a considerable number of finger injuries would be expected. Most, however, would fall into the "lumps, bumps, and bruises" category of injuries and probably would have few sequelae.

This study documents a low injury rate in a local preadolescent basketball program. Youth basketball is not a hazardous sport even when played on linoleum floors. A simple first aid kit should be sufficient to treat most acute traumatic injuries. It is important for such programs to be safe for young athletes so that the goals of the program are achieved. These include the enjoyment of the sport and the development of a positive self-image.¹

I thank Stephanie Roberts of the Charlottesville-Albemarle YMCA and the coaches and site supervisors in the youth basketball program for making this study possible. Jacob Lohr, MD, provided valuable encouragement and editorial suggestions.

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BOOK REVIEW

Parenteral Nutrition in Infants and Children: Basic Principles and Practical Guidelines

By T.M. Ramanujam, 185 pp with illus, \$20, Madras, India, Password Process Pvt Ltd, 1989.

This book provides a stepwise approach to the use of safe parenteral nutrition (PN) in developing countries and presents an overview of PN topics at an elementary level.

The book is divided into two sections. Section 1, "Basic Principles," includes chapters on consequences of malnutrition, general principles of PN, evaluation of nutritional status and requirements, technical considerations in PN, venous access, administration of PN, metabolic response to PN, monitoring, complications, and the role of the nursing staff. The chapters are typically four- or five-page synopses of generally accepted information written in a simple format.

Unfortunately, however, certain information is inaccurate. For example, the statement "[Intravenous dextrose] has a caloric value of 4 kcal/gm [16.8 kJ/g]" is of concern in a book written for persons with a minimal knowledge of PN, because it could lead to undernutrition; carbo-

hydrates have a caloric value of 16.8 kJ/g, but intravenous dextrose has only 14.3 kJ/g. Likewise, the suggestion that solubility problems of calcium and phosphate can be overcome by adding them to alternate bags of PN is disturbing, since this practice has been shown to result in poor retention of both minerals and is, thus, not currently recommended. Stating that insulin can be added to PN is appropriate, but it is an error of omission not to specify that only regular insulin should be used. Statements such as "some administer amphotericin B along with Intralipid" infers that this practice is acceptable, despite no data in current literature to support the compatibility or stability of either component during such administration.

The author provides a discussion and illustrations of the PN preparation method that he uses. This description serves its purpose of providing a guide for practitioners in developing countries, and for others, it provides insight into the conditions faced by these practitioners. More detailed information on types, rates, and management of complications, especially infections, would have complemented the brief discussion of complications. Good diagrams and photographs are included in the chapters on venous access and monitoring, although safer ap-

proaches are now used for some of the techniques demonstrated (eg, femoral access).

Section 2, "Special Problems," includes chapters on management of PN in neonates, diarrhea, inflammatory bowel disease, and gastrointestinal fistulas. Recent advances in PN and the views of the author on PN in developing countries are also presented. The chapters on intractable diarrhea and gastrointestinal fistulas present good, but brief reviews of the subjects. These chapters are greatly enhanced by the pictures of patients before and after PN therapy. The discussion of intestinal tuberculosis is also highlighted by such pictures. Better references, however, would be of benefit in these chapters.

Overall, *Parenteral Nutrition in Infants and Children* would be of limited value to most practitioners. However, the book provides insight into practice conditions and a basic guide for PN preparation in developing countries. Here again, the highlights of the book are the pictures of children before and after PN therapy.

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Decreasing Severity of Chronic Uveitis in Children With Pauciarticular Arthritis

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• We compared the current prevalence and severity of chronic uveitis in children with pauciarticular juvenile rheumatoid arthritis in Seattle, Wash, with that of children with the same condition in the same area in 1975. The prevalence of eye disease decreased from 45% in 1975 to 13% in 1989, and the proportion of patients with severe visual loss decreased from 21% in 1975 to none in 1989. We could not attribute these findings to differences in known risk factors for iritis, such as age, sex, or presence of antinuclear antibodies. There was no difference in the duration of follow-up between the two groups. It is possible that the decline in prevalence of uveitis reflects a referral bias for eye disease in the 1975 population. However, the decrease in disease severity remains unexplained and may represent more effective treatment, earlier surveillance for ocular disease, or a change in the frequency of ocular manifestations of this disease in the 1989 group.

(AJDC. 1991;145:1026-1028)

Chronic uveitis may occur in association with juvenile rheumatoid arthritis (JRA) and is most often observed in young girls with pauciarticular-onset JRA and antinuclear antibodies.¹⁻³ Initially, JRA-associated uveitis is asymptomatic and can only be detected using slit-lamp ophthalmologic examination. However, if untreated, chronic uveitis may lead to synechiae, cataracts, and band keratopathy, all of which can obscure vision.⁴ Past studies suggest that approximately 16% of the eyes affected with JRA-associated uveitis will become blind.⁴⁻⁶

In the 1960s and 1970s, the prevalence of chronic uveitis in patients with pauciarticular JRA varied from 14% to 34% in North American centers other than that in Seattle, Wash (Table 1).^{4,6-10} We were interested in determining whether the prevalence or the severity of JRA-associated uveitis was changing over time. Therefore, we compared the prevalence and severity of chronic uveitis in children with pauciarticular JRA followed up by the University of Washington Pediatric Rheumatology Clinic during 1975 with the prevalence and severity of those followed up by the clinic in 1989.

PATIENTS AND METHODS

All study patients met the American Rheumatism Association's criteria of JRA.¹¹ We restricted this study to children with pauciarticular-onset disease because most patients with JRA-associated uveitis have this type of disease onset.¹⁻¹⁰ The patients were evaluated for evidence of uveitis through periodic ophthalmologic examinations, generally at 3- to 4-month intervals. These examinations were performed by a variety of ophthalmologists; methods of detection of uveitis have not changed during the period of this study. Uveitis was determined by the presence of inflammatory cells or by increased levels of anterior-chamber protein as detected by light refraction during any ocular examination. Data on the prevalence of uveitis in 1975 were derived from data in a previously published report⁸ of children presenting to the Seattle, Wash, clinic. Data on prevalence in 1989 were compiled from records of all active patients with pauciarticular JRA. None of the 1989 patients was an active patient in 1975.

Assays to determine the presence of antinuclear antibodies were performed using standard methods; rat liver was used as substrate in 1975 assays, and Hep-2 cells were used in 1989 assays. Immunoglobulin M rheumatoid factor was assayed using the latex agglutination method.

Data were subjected to χ^2 analyses with Yates' correction using the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Ill).

RESULTS

The 33 patients from 1975 were compared with 134 active patients in 1989 (Table 2). The median age of both groups was less than 4 years, and the percentages of female or antinuclear antibody-positive patients were similar. Thus, the patient groups were comparable in terms of known risk factors of uveitis.¹⁻³ Data on time of onset of uveitis relative to onset of arthritis were unavailable, but duration of follow-up was similar between groups. In 1989, however, the prevalence of chronic uveitis decreased significantly, and the decrease in the prevalence of impaired vision due to uveitis was even more marked. In 1975, seven patients experienced substantial visual impairment, and of these five experienced unilateral or bilateral blindness. In contrast, no child studied in 1989 experienced significant visual loss ($P < .00005$).

COMMENT

Strikingly, severe visual impairment was absent among the children with JRA-associated uveitis seen in 1989 compared with a similar group of children treated in 1975. This is surprising because the 1989 patient group did not

Accepted for publication January 31, 1991.

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Table 1.—Reports of Prevalence of Chronic Uveitis in Children With Pauciarticular Juvenile Rheumatoid Arthritis in the United States

Location of Center	Years of Study	Prevalence (%)	Source, y
Seattle, Wash	1964-1968	7/24 (29)	Schaller et al, ⁷ 1969
Seattle, Wash	1974-1975	15/33 (45)	Schaller, ⁸ 1977
Ann Arbor, Mich	1961-1974	24/133 (18)	Cassidy et al, ⁹ 1977
Boston, Mass	1963-1974	28/83 (34)	Chylack, ⁴ 1977
Dallas, Tex	1974-1975	12/88 (14)	Fink, ¹⁰ 1977
Jersey City, NJ	1960-1970	6/32 (19)	Calabro et al, ⁵ 1970

Table 2.—Comparison of Past and Present Patients With Pauciarticular JRA in Seattle, Wash*

	1974 Patients	1989 Patients	Results of χ^2 Analysis	P
N	33	134
Median age, y	2.2	3.2
Mean follow-up, y	6.0	5.9
Patient characteristics, %				
Female	88	75	1.73	NS
ANA positive	52	70	3.33	NS
RF positive	None	3	0.17	NS
Uveitis	45	13	15.16	.0001
Visual loss	21	None	24.62	<.00005

*JRA indicates juvenile rheumatoid arthritis; NS, not significant; ANA, antinuclear antibody; and RF, rheumatoid factor.

differ from the 1975 group in variables known to confer increased risk of eye disease. There are several possible explanations for this trend. The first is that uveitis may have been identified and treated earlier in the 1989 group than in the 1975 group. Uveitis diagnosed simultaneously with JRA has been associated with a higher risk of visual impairment in the patient; this is thought to be due to the fact that the uveitis has gone untreated for some time.^{12,13} We had no data concerning the onset of uveitis in the 1975 group. Therefore, no precise evaluation of this risk factor could be made. Duration of follow-up is another important variable because visual impairment usually develops over a long period. There was no difference in duration of follow-up between the two groups of patients. It is possible that prompt treatment of uveitis effectively decreased the prevalence of visual impairment. Another possibility is that current techniques of treatment of JRA are modifying the associated eye disease. Although there is no relationship between flares of ocular and articular disease in JRA,^{12,13} anti-inflammatory medications given to treat JRA may reduce ocular inflammation.¹⁴ Thus, earlier referral and more aggressive treatment of arthritis among patients with JRA in 1989 might have reduced the severity of uveitis. It is postulated that autoimmune diseases are initiated by an environmental trigger interacting with a susceptible host. If this paradigm applies to JRA-associated uveitis, the change in severity of uveitis may reflect a change in the virulence of the environmental trigger. In this regard, it is interesting that in New Zealand between 1971 and 1980 there was only one case of mild, remitting iritis among 38 children with pauciarticular JRA.¹⁵ Alternatively, patients with aggressive uveitis may represent a clinical subgroup.^{16,17} Such a subgroup might be associated with a particular human leukocyte antigen type; an association between B15/w62 and severe uveitis has been reported.¹⁶ Other immunologic characteristics, such as titer or class of antibodies to retinal antigen S, may also identify a subgroup of patients with chronic uveitis and poor prognoses.^{18,19}

This study also revealed a reduction in the prevalence of chronic uveitis in children with JRA in the 1989 group. Prevalence of chronic uveitis in children with pauciarticular JRA in Seattle in 1975 was particularly high compared with that of patients in other pediatric rheumatology cen-

ters (Table 1) in other years, raising the possibility that 1975 was an unusual year in this regard. However, the prevalence of uveitis in the 1989 group was also less than half of the 29% prevalence observed in patients of an earlier study conducted in Seattle between 1964 and 1968 (Table 1). During the 14-year span between groups examined in our study, the composition of our patient population likely changed. Most children diagnosed with JRA in our community receive medical attention; this includes those with mild, uncomplicated disease. It is likely that only complicated cases of JRA were referred for medical attention at both earlier reports; chronic uveitis would have constituted such a complication, thus increasing its apparent prevalence in the population with JRA. This is corroborated by the increase in the number of children presenting at our clinic with pauciarticular JRA from 3.22 children per 100 000 children in Washington in 1975 to 11.85 per 100 000 in 1989.²⁰ Given present referral practices, we believe the data from 1989 accurately reflect the current prevalence of chronic uveitis associated with pauciarticular JRA in our region. This level (13%) is similar to earlier findings from several other geographic locations (Table 1). These results suggest that the prevalence of chronic uveitis among patients with pauciarticular JRA is relatively constant.

Data from other centers are necessary to determine if our findings are unique to our region. Rigorous surveillance for asymptomatic chronic uveitis and prompt treatment are still recommended because blindness remains a potential sequela of this disease. Nonetheless, the decreasing severity of JRA-associated uveitis in the Pacific Northwest is reminiscent of milder carditis associated with acute rheumatic fever in the 1960s compared with earlier years²¹ and may indicate that pauciarticular JRA is a dynamic disease with changing manifestations.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Multiple Sclerosis Associated With Vitamin B₁₂ Deficiency

E. H. Reynolds, FRCP; J. C. Linnell, PHD; J. E. Faludy
(*Arch Neurol.* 1991;48:808-811)

Myasthenia Gravis in Childhood and Infancy: Usefulness of Electrophysiologic Studies

Christophe Vial, MD; Nadine Charles, MD; Guy Chauplannaz, MD; Bernadette Bady, MD
(*Arch Neurol.* 1991;48:847-849)

Family History of Myocardial Infarction and Hemodynamic Responses to Exercise in Young Black Boys

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• The influence of family history of coronary artery disease on children's hemodynamic responses to exercise was examined with 25 black boys aged 7 to 10 years. Blood pressure, heart rate, cardiac output, stroke volume, and total peripheral resistance were evaluated during preexercise, peak exercise, and recovery stages. Children with a family history of CAD exhibited greater systolic blood pressure and total peripheral resistance during preexercise and peak exercise stages than did those without a family history of coronary artery disease. After controlling for preexercise differences, the group with a family history of coronary artery disease exhibited greater increases in systolic blood pressure and less attenuation of total peripheral resistance to peak exercise than the group without a family history of coronary artery disease. Cardiac output indexed by body surface area and stroke volumes were higher at all times in the group without a family history compared with the group with a family history of coronary artery disease. Findings are compared with those of adult studies in terms of influence of family history of coronary artery disease on cardiovascular reactivity to stress.

(AJDC. 1991;145:1029-1033)

Coronary artery disease (CAD) continues to be the leading cause of death among black adults in the United States, with mortality rates comparable in black and white men and greater in black women compared with white women.^{1,2} Research indicates that cardiovascular reactivity to stress may play a role in the cause and/or clinical manifestations of CAD.^{3,4} Prospective studies involving both humans and animals indicate that blood pressure (BP) and heart rate (HR) reactivity to laboratory stressors are predictive of atherosclerotic development and CAD-related mortality.^{5,6}

Studies involving children and adults have found that-

blacks exhibit greater BP responses to physical (eg, dynamic exercise and cold pressor task) and psychological (eg, video game challenge task) stressors than do white cohorts.⁷⁻¹² Recent findings indicate that greater levels of total peripheral resistance (TPR) may account for the racial differences in BP reactivity, regardless of whether the stressor is primarily α -adrenergically^{8,12} or β -adrenergically^{9,10} mediated.

A major risk factor for CAD is a family history of the disease.^{13,14} Cardiovascular hyperactivity in response to stress has been associated with family history of CAD in young white adults.^{15,16} To our knowledge, no published studies have assessed this relationship among blacks. Such an evaluation is needed because CAD is a substantial problem among blacks, and blacks exhibit greater reactivity than whites to many stressors.

In this study, we evaluated the cardiovascular responses to dynamic exercise in a healthy group of black children with or without a family history of CAD. Because premature myocardial infarction among first- and second-degree relatives has been strongly associated with later development of CAD,¹⁴ children were classified by presence or absence of myocardial infarction among one or more biological parents or grandparents before 55 years of age. Given on the above findings, we predicted that the black boys with a family history of CAD would exhibit greater increases in BP in conjunction with less attenuation of TPR.

SUBJECTS AND METHODS

Twenty-eight healthy 7- to 10-year-old black boys (14 with and 14 without a family history of CAD) were selected from family health history records obtained from a countywide public school screening of families interested in participating in a longitudinal study of cardiovascular health.¹⁷ The family health history form completed by the parent(s) assessed cardiovascular disease history in the child's biologic parents and grandparents. This questionnaire has been used in previous research from our laboratory and validated with substantial agreements noted between physician records and parental self-reports of family health history.^{12,17}

On arrival at the laboratory, a parent granted informed consent and the child granted assent to participate as approved by our institutional human assurance committee. The parent again completed the family health history questionnaire. Given the age range of the children, parents were relatively young (mean age,

Accepted for publication March 28, 1991.

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Reprints not available.

Table 1.—Anthropometric Variables by Coronary Artery Disease (CAD) History Group*

Anthropometric Variables	CAD— (n = 13)	CAD + (n = 12)
Age, y	8.80 (0.86)	8.64 (1.05)
Height, cm	135.30 (7.60)	135.21 (4.81)
Weight, kg	33.80 (5.20)	32.78 (5.29)
Body surface area, m ²	1.11 (0.08)	1.11 (0.18)
Quetelet index, kg/m ²	18.40 (1.80)	17.90 (2.40)

*CAD— indicates no family history of CAD; CAD+, family history of CAD. Values are mean (SD).

33.2 years for those without and 35.7 years for those with a family history of CAD, $P > .15$), and all biologic grandparents were older than 55 years. None of the children's biologic parents or siblings were reported to have experienced a myocardial infarction. Parents of two subjects were unsure of the age at the time of myocardial infarction in the child's grandparent. Therefore, these children's data were excluded from the analyses. Complete information concerning history of myocardial infarction was obtained for all parents and grandparents of the remaining subjects.

Although family history of essential hypertension has been associated with greater cardiovascular reactivity to laboratory stressors among white children and adults, only a few studies have evaluated this issue among blacks.¹⁸ A family history of hypertension has not been associated with increased reactivity in black adults in response to β -adrenergic-mediated stressors.¹⁹ However, Musante et al¹⁸ recently found that among black male children, those with family histories of hypertension exhibited greater cardiovascular reactivity to an α -adrenergic-mediated stressor of forehead cold stimulation.

Given the high prevalence rates of essential hypertension among blacks, especially in the Southeast,²⁰ it was not feasible to exclude from recruitment children from families with hypertension. Thus, 50% of the subjects with a positive family history had at least one parent with hypertension, as did 23% of subjects with a negative family history. Likewise, 93% of the subjects with a family history and 31% of subjects without a family history of CAD had at least one grandparent with hypertension. By using the classification system previously described, a more conservative approach is being used, ie, if family history of hypertension is related to reactivity to the β -mediated stressor of exercise, there is less likelihood of finding substantial differences because the negative history group included children from families with parents and/or grandparents with hypertension.

Each child received a complete cardiovascular examination by a pediatric cardiologist to help exclude cardiac disease. No child was a trained athlete. Children's height and weight were measured, and hematocrit readings were assessed. Body surface area was calculated with the formula of DuBois and DuBois.²¹ Criteria for exclusion included body surface area less than the third or greater than the 97th percentile for age²²; current illness, including sickle-cell disease and/or anemia (ie, hematocrit < 0.32); and a resting BP greater than the 90th percentile for age.²³ Based on these criteria, one child was excluded from participation.

Exercise was performed on an exercise table with an electronically braked cycle ergometer (Quinton Table Ergometer Model 8464, Quinton Inc, Seattle, Wash). Children were placed in the supine position, and an appropriate-sized BP cuff for use with an automated BP monitor (Dinamap Monitor Model 1165, Critikon Inc, Tampa, Fla) was placed on the right arm. Electrocardiographic leads for monitoring and timing of the HR and echocardiographic and Doppler measurements (Hewlett-Packard Model 7020AC, Hewlett Packard Inc, Atlanta, Ga) were also attached. The supine position was chosen because it provides a better acoustic window for ultrasound evaluation, because the ascending aorta remains posterior and the subject is

relatively immobile. With the use of this technique, the findings obtained were comparable with those of other child studies involving upright cycle ergometer exercise with similar peak responses for physical working capacity index.²⁴

Following a 5-minute rest period, preexercise measurements of HR, BP, aortic valve systolic area, and velocity of ascending aortic blood flow were made. Children were then urged to pedal an electronically braked ergometer until exhausted with use of a graded protocol previously established in our laboratory. The protocol included increasing workloads of 3 minutes' duration that were predetermined on the basis of body weight.⁷

Systolic and diastolic BP (SBP and DBP) were assessed during the last 30 seconds of the preexercise rest period, during each exercise stage, and 3 to 5 minutes following cessation of exercise. Mean arterial pressure (MAP) was calculated as follows: $[SBP + (2 \times DBP)]/3$. The BP monitor has been validated for use during dynamic exercise testing with children of this age range.²⁵ Heart rates were recorded at the same points in time described above from electrocardiography with the R-R interval.

The Doppler echocardiographic assessment technique has been used by other investigators^{26,27} and is presented in detail in reports of other studies from our laboratory.^{12,24} Briefly, during the preexercise stage, two-dimensional guidance directed an M-mode beam for measurement of aortic leaflet separation at the sinuses of Valsalva during systole. This measurement of aortic leaflet separation was used for calculation of all cardiac output (CO) values. Aortic flow area (AA) was calculated as follows: $AA = [(1/2) \text{ diameter}]^2 \times 3.14$ (reported in square centimeters). Doppler examination was performed concurrently with the BP and HR assessments with the use of a 1.9-MHz continuous-wave transducer placed in the suprasternal notch and directed toward the aortic valve with the beam positioned to achieve maximum flow velocity. Measurement of maximum flow velocity was made simultaneously with the other cardiovascular measurements. Computer analysis of the Doppler reading was employed to measure the peak velocity, flow velocity integral, and mean velocity at each assessment point along with the corresponding ejection times. From these values, CO was calculated as follows: $CO = (V/2)(ET \times HR) \times AA$ (where V indicates velocity in centimeters per second [$V/2$ = average velocity]; ET, ejection time in seconds; and HR in beats per minute, with AA reported in square centimeters and CO reported in milliliters per minute). Cardiac index (CI) was calculated by dividing CO by body surface area. Rate pressure product (RPP) was calculated as follows: $RPP = HR \times SBP$ (expressed in beats per minute per millimeters of mercury). Stroke volume was calculated by dividing CO by HR. Total peripheral resistance was recorded in Wood units (ie, $TPR = MAP/CI$) and reported as millimeters of mercury per liter per minute per square meter.

RESULTS

Anthropometric Data

Means and SDs of anthropometric data for the two groups are presented in Table 1. Analyses revealed no significant differences between the groups in age, height, weight, body surface area, or body mass (ie, Quetelet Index) (all $P > .54$).

Physical Working Capacity

The maximum physical working capacity (aerobic power) was indexed by body weight in kilograms and was not significantly different between the groups (group without a family history of CAD, 17.8 ± 2.7 kg/min per kilogram [mean \pm SD]; group with a family history of CAD, 17.9 ± 2.5 kg/min per kilogram; $P > .96$). These values are consistent with the 50th to 75th percentile values obtained in previous upright cycle ergometer studies in our laboratory with boys of this age range.⁷

Table 2.—Hemodynamic Responses During Preexercise, Peak Exercise, and Recovery Stages by Coronary Artery Disease (CAD) History Group*

Hemodynamic Variable	Preexercise		Peak		Recovery		Effects†
	CAD–	CAD+	CAD–	CAD+	CAD–	CAD+	
Heart rate, BPM	74.7 (9.9)	80.8 (14.4)	178.8 (23.7)	174.3 (18.1)	107.4 (13.8)	110.0 (15.1)	B
Blood pressure, mm Hg							
Systolic	109.8 (10.1)‡	120.9 (10.7)	147.6 (16.3)§	166.0 (23.1)	123.5 (16.1)	119.9 (11.5)	B, C
Diastolic	72.8 (9.9)	75.3 (12.8)	78.3 (13.4)	77.9 (16.3)	68.3 (12.0)	65.9 (10.5)	B
MAP	85.2 (7.8)	90.5 (10.5)	101.4 (9.4)	107.9 (11.8)	86.7 (12.0)	83.9 (8.8)	B
Cardiac index, L/min per m ²	2.46 (0.43)‡	2.04 (0.48)	5.88 (1.28)	4.93 (1.26)	4.15 (0.99)	3.47 (0.91)	A, B
Total peripheral resistance, mm Hg/L per min per m ²	29.06 (5.79)‡	38.6 (12.5)	14.7 (4.45)§	19.7 (5.88)	18.02 (5.55)	21.72 (6.83)	A, B
Stroke volume, mL/BPM	37.4 (9.2)‡	29.4 (8.2)	37.1 (9.8)§	30.9 (5.8)	43.8 (12.8)	35.6 (8.7)	A, B
Rate pressure product, BPM mm Hg	8394.7 (886.3)‡	9747.2 (1829.9)	26 500.8 (4972.1)	28 969.4 (5502.9)	13 391.9 (3090.6)	12 863.2 (1703.4)	B

*CAD– indicates no family history of CAD; CAD+, family history of CAD; BPM, beats per minute; and MAP, mean arterial pressure. Values are mean (SD).

†A indicates main effect for family history of CAD (all $P < .05$); B, main effect for stage of exercise (all $P < .01$); and C, family history by stage of exercise interaction effect ($P < .01$).

‡Significant difference at preexercise stage, as determined by univariate testing (all $P < .05$).

§Significant difference at peak exercise, as determined by univariate testing (all $P < .05$).

Hemodynamic Responses to Exercise

The means and SDs for all hemodynamic responses during preexercise, peak exercise, and recovery stages for each group are presented in Table 2. A series of 2 (negative and positive family history) \times 3 (preexercise, peak exercise, and recovery) repeated measures analyses of variance with Greenhouse-Geisser corrections²⁸ were conducted for each hemodynamic response. With these two-way analyses of variance, three terms are tested for statistical significance (ie, family history [negative or positive], stage of exercise [preexercise, peak, or recovery], and the family history \times stage of exercise interaction). If the interaction is significant, it means that the two groups do not show the same pattern of response across the various stages of exercise. A significant main effect for family history would (in the absence of a significant interaction) mean that one group showed a higher level of response at all stages of exercise. A significant main effect for stage of exercise would indicate that both family history groups exhibited the same pattern of significant changes in cardiovascular responses to exercise.

As illustrated in Table 2, exercise produced the expected changes in all hemodynamic responses. This was verified by significant stage of exercise main effects for all hemodynamic responses (all $F > 5.3$, all $P < .01$), indicating that exercise caused significant increases in SBP, DBP, MAP, HR, stroke volume, RPP, and CI, while TPR decreased.

HR

No significant differences were obtained between the groups at preexercise, peak exercise, or recovery stages (all $P > .20$). Likewise, the group \times stage interaction was not significant ($P > .26$).

BP

A significant interaction effect was observed between family history and stage of exercise for SBP ($F[2,42] = 6.2$, $P < .005$), with the positive family history group exhibiting greater SBP at preexercise ($P < .02$) and peak exercise ($P < .03$) stages, but not at recovery ($P > .53$). No family history \times stage interaction or family history main effect approached significance for DBP or MAP (all $P > .18$). No significant differences between the groups were noted for DBP or MAP at preexercise, peak exercise, or recovery stages (all $P > .13$).

CI

A significant family history main effect was obtained ($F[1,23] = 5.9$, $P < .02$). As shown in Table 2, the negative family history group exhibited a greater CI at all times. These differences were 0.42 L/min per square meter at preexercise, 0.95 L/min per square meter at peak exercise, and 0.68 L/min per square meter at recovery.

TPR

A significant family history main effect was noted ($F[1,21] = 6.1$, $P < .02$). The positive family history group produced greater TPR with mean differences greatest during preexercise (9.5 mm Hg/L per minute per square meter) followed by peak exercise and recovery (5.0 and 3.7 mm Hg/L per minute per square meter, respectively). The group \times stage interaction was not significant ($P > .25$).

Stroke Volume

A significant family history main effect was observed ($F[1,23] = 6.0$, $P < .02$), with the negative family history group found to exhibit higher stroke volume across all phases, as illustrated in Table 2. Mean differences between the two groups at preexercise, peak exercise, and

recovery stages were 8.0, 6.2, and 8.2 mL per beats per minute, respectively. The group \times stage interaction was not significant ($P > .64$).

RPP

The positive family history group exhibited higher RPP during preexercise only ($P < .05$). Neither family history nor the family history \times stage interaction approached significance (both $P > .24$).

Additional Analyses

Because there were preexercise differences between the groups in terms of SBP, TPR, and stroke volume, data from peak exercise and recovery stages were reanalyzed with analyses of covariance using the respective preexercise values as covariates. For SBP and TPR, the results were similar to those of the unadjusted analyses with the positive family history group exhibiting larger increases in SBP ($F[1,20] = 9.73$, $P < .005$) and less attenuation of TPR ($F[1,20] = 4.5$, $P < .05$). No significant differences were observed for stroke volume ($P > .51$).

COMMENT

Individuals with a positive family history of CAD have been found to exhibit greater hemodynamic reactivity to laboratory stressors.^{15,16} These studies have typically involved young white adults.^{15,16} Seven- to 10-year-old black boys were the subjects of our study. Boys who had a family history of CAD exhibited greater SBP and TPR at preexercise and peak exercise stages than did boys who had no family history of CAD. Adjustment for these preexercise differences indicated that the positive family history group exhibited greater increases in SBP and less attenuation in TPR in response to exercise.

Total peripheral resistance is a calculated value; it is inversely related to CO and is directly related to MAP. The greater TPR of the boys in the positive family history group at preexercise and peak exercise was associated with a lower CO. Although the boys in the positive family history group had a lower CI at peak exercise than those in the negative family history group, their power output was the same. This suggests the possibility of a more efficient cardiovascular system in the boys in the positive family history group. However, because their SBP and myocardial tension were higher, as expressed by the RPP, myocardial oxygen consumption should have been higher as well. Sarnoff et al²⁹ has demonstrated that myocardial tension is directly related to the RPP. At peak exercise, the RPP in boys with a family history of CAD was comparable with the boys without a family history of CAD. This suggests that each group achieved the same functional result through different mechanisms. The boys in the positive family history group achieved their power output with a lower HR response. Their peak HR response was slightly less than that in boys in the negative family history group, but their SBP was significantly greater. These responses are consistent with a baroreceptor hypothesis that suggests that individuals with a family history of CAD may possess an intrinsically greater vascular tone. The prolonged effect of long-term increased myocardial tension on a child's myocardium is unclear.

Because the boys with a positive family history demonstrated greater SBP at preexercise related to both lower CI and higher TPR, there is a strong suspicion that there is an inherent difference in autonomic regulation of the circulatory responses. The consistency of these findings with those of a previous study²⁴ strongly suggests differ-

ences in autonomic control of the circulatory system. In that study 10-year-old black boys exhibited greater TPR during preexercise, peak exercise, and recovery stages than white boys. The influence of family history on the hemodynamic response differences was not assessed.²⁴

There was a trend toward greater CI in the boys with a negative family history than in those with a positive family history at peak exercise and recovery. The magnitude of change in CI from resting to peak and from peak to recovery were similar in the two groups. For the negative family history group, CI increased by 239% from resting to peak, and for the positive family history group the increase was 242%. This suggests that the two groups responded similarly in their CI response to the demands of exercise, although the positive family history group began at a lower level. From peak exercise to recovery, CI in both groups decreased by 30%. This reinforces the likelihood that their CI responses to the metabolic requirements of the task were similar. Therefore, the elevation in the TPR of the boys in the positive family history group may be secondary to an increase of vascular tone (resistance). This suggests that the primary difference in the boys with a positive family history of CAD is increased TPR secondary to increased vascular tone and is not caused by a lower CI, which appears to vary appropriately with the metabolic requirement.

Differences in cardiovascular responses between the two groups may be due in part to factors related to family history of essential hypertension. However, this is unlikely, as several subjects in the negative family history group had family histories of hypertension and not all subjects in the positive family history group had a positive family history of hypertension. On the other hand, perhaps combined effects of family history of early myocardial infarction and essential hypertension have additive, multiplicative, or symbiotic effects on children's cardiovascular responses to stress. The sample size of our study does not permit adequate evaluation of this issue. Research is warranted to address the separate and combined effects of a history of both CAD and essential hypertension in first- and second-degree relatives on children's hemodynamic responses to laboratory stressors.

Perhaps the blacks with a positive family history in our study are not only more likely to exhibit exaggerated BP reactivity to stress but are also more prone to exhibit physiologic reactivity to the laboratory conditions and situations surrounding the test itself. Other findings indicate that blacks compared with whites exhibit greater pressor responses to the mere presence of laboratory personnel and the surrounding laboratory environment.^{9,19} Young adults who have a positive family history have been found to exhibit higher prestressor BP during competitive stressor tasks compared with negative history cohorts.¹⁶ Thus, prestressor cardiovascular response differences may be due to the positive family history group experiencing greater anticipatory anxiety and relaxation difficulties.

The possibility also exists that the preexercise BP differences were due to differences in hemodynamic regulatory mechanisms between the two groups. Structural changes in the vasculature may have already occurred in the positive family history group, possibly due to genetic predisposition and/or early effects of environmental stress. Other differences between the two groups might be responsible for the preexercise BP differences, including differences in sodium, potassium, and calcium intakes and their influence on arteriolar smooth-muscle activity.³⁰

Future studies should address these possibilities with attention to the establishment of adequate baseline levels before subjects are exposed to various stressors. One approach that would alleviate prestressor differences between groups related to anticipatory anxiety is that used by Obrist et al³¹ in which subjects' baseline measures are established in a separate session after exposure to the stressor.

The current findings add to the accumulating evidence^{8-10,12,24} that greater BP responses to physical and psychological stress among blacks may be due to greater TPR, even if the stressor is primarily β -adrenergic mediated, as in our study. Prospective studies are needed to determine whether individuals with a family history of cardiovascular diseases (ie, CAD and/or essential hypertension) who also exhibit exaggerated cardiovascular reactivity to stress are more likely to develop earlier clinical manifestations of other markers of cardiovascular disease (eg, left ventricular hypertrophy and S-T segment changes on echocardiography). Such studies will help identify mechanisms involved in the development of cardiovascular diseases and will permit the development of effective intervention programs (eg, physical activity and stress management as buffers against hemodynamic reactivity to stress) that could be incorporated into the pediatrician's armamentarium to promote a healthier population of children and to help prevent adult onset of cardiovascular diseases.

This research was supported by grants HL41781 and HL35073 from the National Institutes of Health, Bethesda, Md, and research grant awards from the Research Institute and Department of Pediatrics at the Medical College of Georgia, Augusta, and the Fraternal Order of Eagles Chapter 1197, Augusta, Ga.

The authors thank Pamela Hawkins for secretarial assistance, Thomas Rhodes for statistical support, and Bonnie Hadden, RCT, Pauline Asihene, Jennifer Kenrick, Leonteen McNeal, Jinny Smith, Paula Williams, and Ellen Wilson, MS, for assistance in data collection.

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Physiologic Responses to Playing a Video Game

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• The displacement of sports and other physical activities by television and video may contribute to the associations among television viewing, obesity, and reduced physical fitness. Because video games are widely played by children and adolescents, we assessed the metabolic and cardiovascular responses to video game playing. Heart rate, blood pressure, and oxygen consumption were measured serially over 30 minutes in 32 males and females aged 16 to 25 years (mean \pm SEM, 20 ± 1 years) while they played the "Ms Pac-Man" video game under standard laboratory conditions and compared with measurements made in a standing but inactive position. Playing the video game significantly increased heart rate, systolic and diastolic blood pressure, and oxygen consumption. Energy expenditure increased from 6.08 ± 0.24 kJ/min while the subjects stood inactive to 10.94 ± 0.49 kJ/min while they played. The increase in metabolic rate and cardiovascular stimulation was similar in magnitude to mild-intensity exercise.

(AJDC. 1991;145:1034-1036)

Reduced physical activity has been associated with obesity in childhood and adolescence, although the question of whether obesity precedes or is a consequence of inactivity remains.¹ Television viewing may indirectly contribute to obesity in American youth by several means, including sedentary behavior with the associated reduction in energy expenditure, as well as increased food consumption.^{2,3} Also, in settings that lacked television, the introduction of television displaced sports.^{4,5}

American children and adolescents spend more than 20 hours per week watching television.⁶ In addition, they spend considerable time playing arcade and home video games. The recent increase in sales of home video games suggests that the time spent playing these games has also increased substantially, although firm estimates are lacking. In contrast to the experience with video games a decade ago,⁷ the newer video games appear to retain their users' interest over time.

In view of the current popularity of video games, a

quantitative assessment of the metabolic and cardiovascular stimulation associated with playing these games is warranted. To our knowledge, no evidence exists that suggests a linkage between obesity and video games. These games involve a degree of isometric muscular contraction and mental stress, both of which could elevate energy expenditure, heart rate, and blood pressure. Previous studies have documented the increases in heart rate and blood pressure induced by playing a television video game,^{8,9} but the energy expended while playing one of these games has not been studied previously, to our knowledge. The objective of this study was to quantify the energy cost and cardiovascular responses to video game playing.

SUBJECTS AND METHODS

Subjects

Twenty males and 12 females between ages 16 and 25 years (mean \pm SEM age, 20 ± 1 years) participated in this study. The subjects were healthy, normotensive nonsmokers. All subjects had some experience playing video games. The study protocol was approved by the Institutional Review Board.

Procedures

The arcade version of "Ms Pac-Man" (Bally Midway Corp, Franklin Park, Ill) was used in this study. Prior to the test session, time was allotted for the subjects to become familiar with playing while breathing through the mouthpiece and breathing valve used for metabolic measurements. Baseline resting measurements were obtained while the subjects stood quietly in front of the video machine for 30 minutes. Oxygen consumption ($\dot{V}O_2$) was measured with open circuit respirometry. The assessment consisted of three measures of 5 minutes' duration each at 5, 15, and 25 minutes within the 30-minute baseline period. The subjects breathed through a low-resistance, one-way valve (Hans Rudolph, Kansas City, Mo). The volume of air was measured with a spirometer (Parkinson-Cowan CD-4, Braintree, Mass), and the expired air was collected in meteorological bags and passed through an infrared carbon dioxide (Beckman LB-2, Fullerton, Calif) and polarographic oxygen (Applied Electrochemistry S-3A, Sunnyvale, Calif) analyzer. Oxygen consumption, carbon dioxide production ($\dot{V}CO_2$), minute ventilation, and the respiratory quotient ($RQ = \dot{V}O_2 / \dot{V}CO_2$) were calculated following standard procedures. Energy expenditure was estimated using the nonprotein energy equivalent for oxygen derived from the Weir equation¹⁰: $kJ = 4.2 \times \{[(RQ \times 1.1) + 3.9] \times \dot{V}O_2\}$.

Brachial artery blood pressure was measured using an aneroid sphygmomanometer, and heart rate was measured with electrocardiography.

The subjects were familiar with the objectives of the game. After a 15-minute warm-up, the subjects played continuously for

Accepted for publication January 23, 1991.

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Physiologic Responses to Playing a Video Game		
Response	Resting (Mean \pm SEM)	Playing (Mean \pm SEM)
Metabolic rate, kJ/min*†		
All subjects	6.08 \pm 0.24	10.94 \pm 0.49
Males	6.67 \pm 0.23	11.71 \pm 0.59
Females	5.10 \pm 0.25	9.68 \pm 0.73
Oxygen consumption (V_{O_2}), mL/kg per min		
All subjects	4.34 \pm 0.09	7.82 \pm 0.29
Males	4.41 \pm 0.12	7.76 \pm 0.36
Females	4.21 \pm 0.14	7.93 \pm 0.48
Heart rate, beats/min*		
All subjects	75 \pm 2	103 \pm 2
Males	73 \pm 2	99 \pm 2
Females	78 \pm 3	109 \pm 3
Blood pressure, mm Hg		
Systolic*		
All subjects	121 \pm 2	138 \pm 3
Males	122 \pm 2	139 \pm 2
Females	120 \pm 4	137 \pm 3
Diastolic*		
All subjects	83 \pm 2	89 \pm 2
Males	83 \pm 2	89 \pm 2
Females	81 \pm 3	88 \pm 2

* $P < .05$ for resting vs playing.

† $P < .05$ for males vs females.

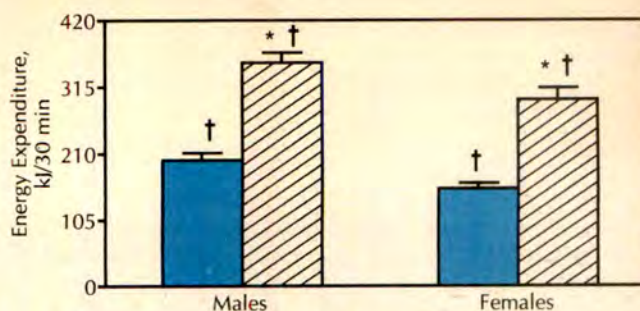
a 30-minute test period, during which three 5-minute measurements of oxygen consumption were made, beginning at 5, 15, and 25 minutes. The validity and reliability of indirect calorimetry in our laboratory have been described previously.¹¹ Heart rate and blood pressure were measured during each of the three oxygen consumption measurement periods. In some cases, the timing of the measurements was adjusted to accommodate interruptions in the players' activity, such as lulls between stages in the game or between games. The scores achieved for complete games were recorded and averaged for each subject.

Design and Statistical Analyses

Analyses of variance performed with repeated measures on the data obtained from the three 5-minute measurements during the periods while the subjects either stood but were inactive or played the video game indicated that time had no significant effect on the physiologic responses (ie, heart rate, blood pressure, and oxygen consumption). Therefore, the mean values of the three measurements were used in subsequent data analyses. Two-way analyses of variance with repeated measures,¹² using sex (male vs female) and activity (resting or playing), were applied to the data to test whether heart rate, systolic and diastolic blood pressure, and energy expenditure were significantly different while the subjects were playing the game than when they stood in front of the machine but were inactive. Pearson's product-moment correlation coefficients¹² were computed to study the relationships among such variables as age, game score, and the increases in heart rate, blood pressure, and energy expenditure.

RESULTS

Heart rate, systolic and diastolic blood pressure, and V_{CO_2} were significantly higher when the subjects were playing the game than when they stood quietly in front



Energy expenditure of males and females during 30 minutes of standing at rest (open bars) and playing a video game (hatched bars). Energy expenditure was greater for males than females under both conditions because of their greater body weight, but the proportional increase in metabolic rate was similar. The asterisk indicates $P < .01$ for rest vs playing; and dagger, $P < .05$ for males vs females.

of the machine (Table). No differences were found between males and females with respect to heart rate or blood pressure either at rest or while playing the video game. Although absolute energy expenditure at rest and while playing the video game was greater for males than females because of their greater body weight (mean \pm SEM body weight, 74 \pm 3 kg vs 60 \pm 3 kg), the magnitudes of the differences between the resting and active values were similar for males and females. Also, when the data were expressed relative to body weight, the responses of the males and females were similar (Table). The energy expended by males and females during 30 minutes of resting and playing the video game is shown in the Figure.

The increase in energy expenditure while playing was correlated with the increase in systolic blood pressure ($r = .64$, $P < .001$), perhaps because of the isometric activity and small muscle mass involved. Game score, an index of performance, and age were uncorrelated with any of the physiologic response variables.

COMMENT

The primary finding of this study was that video games are not a passive activity and the energy cost of the game approximates mild-intensity exercise. The energy cost of playing the video game was similar to that of walking at a pace of ≈ 2.0 mph.¹³ Despite the potentially beneficial effects of video games on energy expenditure, video games are clearly not a substitute for more intensive exercise because the level of cardiorespiratory stress from playing the video game is not sufficient to improve cardiorespiratory fitness.¹³ Furthermore, other aspects of video games may have adverse effects, such as "Nintendo epilepsy,"¹⁴ a photoconvulsive response to the video game image, or "nintendinitis,"¹⁵ tendinitis attributable to excessive playing of video games.

The increase in energy expenditure while playing was correlated with the increase in systolic blood pressure ($r = .64$, $P < .001$), perhaps a result of the relatively small muscle mass and isometric activity of hand grip involved in playing the video game. The increase in systolic blood pressure from playing the video game was greater than would be observed for the same degree of V_{O_2} during an exercise that involves the whole body, such as walking.¹⁶

Although television video games may displace sports and other physical activities that involve a far greater en-

ergy expenditure among American youth, the associations among television viewing, reduced physical fitness, and obesity are probably not otherwise attributable to time spent playing video games. The effects of playing video games on energy expenditure suggest that it is not a passive activity, and may not have the same effects as television has on the prevalence of obesity.

The results of this study demonstrate that playing an arcade-quality video game increases energy expenditure by roughly 80%, but does not provide sufficient cardiorespiratory stress to improve physical fitness in youth.

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In Other AMA Journals

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Anomalous Coronary Arteries Arising From the Aorta Associated With Sudden Death in Infancy and Early Childhood: An Autopsy Series

Jill Lipsett, MBBS, PhD; Roger W. Byard, MBBS; Blair F. Carpenter, MD; Cita L. Jimenez, MD; Anthony J. Bourne, MBBS
(*Arch Pathol Lab Med*. 1991;115:770-773)

Arterial Catheter-Related Infections in Children

A 1-Year Cohort Analysis

Susanna Furfaro, MD; Marie Gauthier, MD; Jacques Lacroix, MD; Daniel Nadeau, MD;
Lucette Lafleur, MD; Sylvain Mathews, MD

● To determine the incidence of infection secondary to arterial catheterization in children as well as the risk markers, we prospectively evaluated, during a 1-year period, all arterial catheters installed in children admitted to the pediatric intensive care unit. A total of 340 cannulas were placed in 310 children aged 80 ± 4 months (mean \pm SEM) for a period of 64 ± 4 hours. Most catheters were inserted percutaneously (99%) in the radial artery (86.5%). Ninety-two percent (313/340) of the catheters were sterile (group 1), 5% (17/340) were contaminated (<10 colony-forming units on semiquantitative culture) (group 2), and 3% (10/340) were considered either locally infected (ie, ≥ 10 colony-forming units) (eight of 10) or associated with a possible catheter-related sepsis (two of 10) (group 3, or infected group). The incidence of local inflammation at the insertion site was higher in group 2 than in group 1 (18% vs 2.9%) but not statistically different between groups 3 and 1 (10% vs 2.9%). The duration of arterial catheterization was longer in group 3 than in group 1 (125 ± 31 vs 61 ± 4 hours). The risk of infection was nonexistent in the first 48 hours of catheterization. Thereafter it was calculated as being 6.2% (10/161), but it correlated poorly with the duration of arterial catheterization. These results confirm the very low incidence of infection related to arterial catheterization in children. Thus, routine catheter reinsertion is, in our opinion, unjustified.

(AJDC. 1991;145:1037-1043)

Patients in intensive care units are at an elevated risk of developing nosocomial infections compared with the general hospital population; this is particularly true for young children.^{1,2} These infections are mainly associated with some type of invasive monitoring or lifesupport

system.^{1,2} It thus becomes very important to determine the infectious risk associated with each of these procedures.

Arterial catheters are now considered a significant cause of catheter-related infection and septicemia in adults.³ In the pediatric intensive care unit (PICU), arterial catheterization has become indispensable for hemodynamic monitoring purposes, and its use has increased sharply in the past 10 to 15 years. No prospective study with systematic cultures of arterial cannulas was available in the pediatric literature except for one performed during the neonatal period,⁴ until we showed that the incidence of infection related to arterial catheterization was low in children.⁵ However, this preliminary study was performed on a small sample of arterial catheters (70 catheters). This study was undertaken to determine more precisely the incidence of infection related to arterial catheterization in children and to characterize the risk markers.

PATIENTS AND METHODS

From September 15, 1988, through September 14, 1989, all children admitted to the St-Justine Hospital PICU and who required an arterial catheterization were included in this study.

Catheter Management

All catheter insertions were performed in the PICU or in the operating room. In most cases, an attempt was made to cannulate the radial artery percutaneously with a 2.5-cm, 22-gauge or a 3.2-cm, 20-gauge Teflon-coated catheter. If radial insertion was impossible, other sites were tried, usually the pedal, femoral, or brachial arteries. When percutaneous cannulation failed, the catheter was inserted by surgical cutdown. Techniques of insertion and site dressing have previously been described⁵; after insertion, catheters were covered with an adhesive taping without topical antibiotic or antiseptic ointments.

Catheter patency was ensured by the continuous infusion of heparinized saline solution (3 mL/h) through a continuous flow device located just distal to the transducer (Fig 1).⁵ As in our previous study, two different arterial blood sampling systems were used: an extension set with T-connection (system A) or a check valve extension set with T-connection (system B).⁵

No component of the entire system, including the dressing, was changed during the study period unless it was found defective.

Accepted for publication January 28, 1991.

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Presented in part at the 10th International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium, March 1990.

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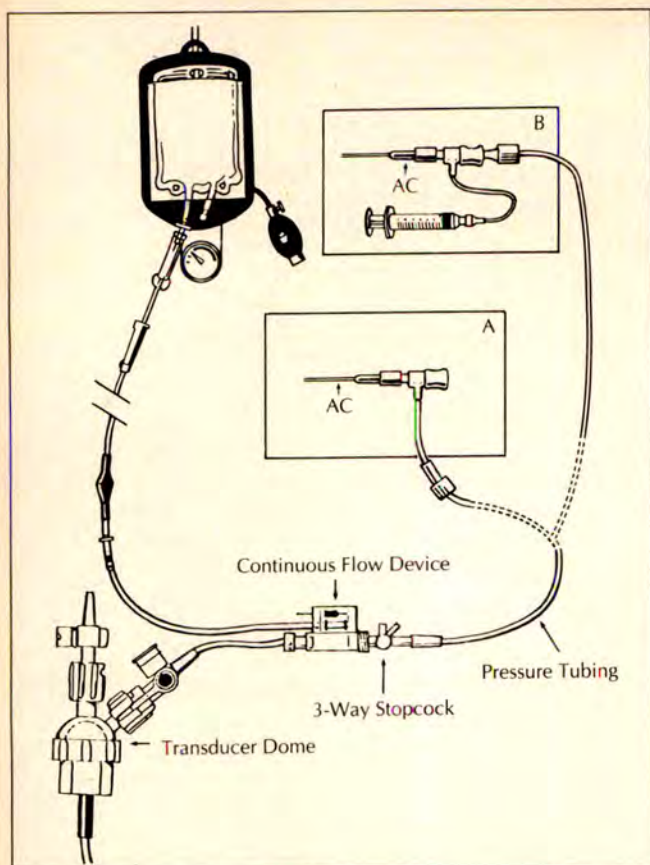


Fig 1.—Diagram of the arterial line system (modified from Du-
charme et al⁵). AC indicates arterial catheter.

Study Protocol

The decision to remove the catheter was made by the patient's physician. When the catheter was no longer required, it was removed aseptically by an attending intensive care unit physician or nurse after local cutaneous disinfection with a 70% alcohol swab. The site was examined for the presence of local inflammation and purulence. The distal 2-cm segment of the catheter was cut with sterile scissors and placed in a sterile transport tube. If within 4 hours before catheter removal, a body temperature over 38.3°C was noted or clinical sepsis was suspected, a blood culture was obtained by venipuncture and 6 mL of infusion fluid was sampled from the nearest stopcock. Both were sent to the laboratory in broth blood culture bottles (Columbia; Chemical Products BDH Inc, Darmstadt, Germany).

In the laboratory, the 2-cm catheter segment was rolled on a blood agar plate by means of the semiquantitative (SQ) method described by Maki et al.⁶ Our protocol for culturing the catheters has already been reported.⁵

For each catheter, the following data were noted: demographic information; conditions predisposing to infections, such as neutropenia (neutrophil count, $<1.0 \times 10^9/L$ on any complete blood cell count during catheter insertion), documented immunodeficiency, corticosteroid therapy (more than 7 consecutive days of systemic steroid use within the month before catheter insertion), or other immunosuppressive therapy (more than 7 consecutive days of immunosuppression within the month before catheter insertion); systemic antimicrobial therapy given while the catheter was in place; all data on any suspected or proved infections of other sites; the mode (percutaneous vs cutdown), location (operating room or PICU), and site (radial, etc) of insertion; the system of arterial blood sampling (see above); the reason for removal; and the number of hours the catheter had been in place. The number of cannulation attempts required before each insertion was not recorded.

Definitions

Inflammation of the catheter site was diagnosed in the presence of lymphangitis, purulence, or at least two of the following: erythema, tenderness, increased warmth, or induration.⁷ Local infection of the catheter site was defined as a positive SQ culture of the distal segment that yielded 10 or more colony-forming units (CFUs). A catheter was considered contaminated if between 1 and 9 CFUs were identified on SQ culture. A catheter tip with a positive broth culture but a negative SQ culture was considered neither infected nor contaminated and was therefore classified as negative. Catheter-related septicemia (CRS) was characterized by all the following criteria: (1) isolation of the same species of microorganism in significant number (≥ 10 CFUs) on SQ culture of the catheter and blood cultures obtained by separate venipuncture; (2) clinical and microbiologic data that disclosed no other apparent source of the bacteremia or fungemia; and (3) clinical features consistent with bloodstream infection.⁷ Possible CRS was defined as follows: (1) isolation of a microorganism in significant number (≥ 10 CFUs) on SQ culture of the catheter; (2) clinical and microbiologic data disclosing no other apparent source of infection; and (3) clinical features consistent with bloodstream infection. Clinical features were considered consistent with a bloodstream infection if a patient was sufficiently ill to warrant a septic workup, including at least a blood culture, and the introduction of systemic antibiotics while culture results were awaited. To diagnose a septicemia due to contaminated infusate and a catheter-related septicemia from other infected sites, we used the definitions of our previous study.⁵

Statistical Analysis

The significance of differences in characteristics among the various groups (cultured and noncultured, with and without contamination, with and without catheter-related infection) was determined by means of χ^2 with Yates' correction for discrete data (χ^2 without Yates' correction if $df > 1$) and two-tailed Student's *t* test for continuous data. $P < .05$ was considered adequate to reject the null hypothesis. Mean values are presented with SEM.

Epidemiologic Analysis

Cumulative survival analysis⁸ and calculations of the density of incidence of infectious complications⁹ were based on epidemiologic methods described previously. For the cumulative survival analysis, the starting event was catheter placement and the terminal event was catheter infection. By definition, catheter infection was diagnosed on removal. The density of incidence of infectious complications per 10 000 hours of insertion was calculated for each day of insertion as follows: Density of incidence of infectious complications = [(cumulative number of infections) \times 10 000] / cumulative number of hours of insertion. For example, up to day 4, five infections (local infection of the catheter site and possible CRS) had been diagnosed. For day 4, the density of incidence of infectious complications was thus the following: $(5 \times 10\,000) / (1255 + 3386 + 4205 + 2559)$, or 4.4. In this equation, the four numbers of the denominator represent the total number of hours of insertion for the catheters removed on days 1, 2, 3, and 4.

RESULTS

During the 1-year study period, 411 arterial catheters were inserted in 361 children. Of these catheters, 71 (17.5%) were not cultured because of accidental removal, contamination on withdrawal, or a failure to send the distal segment of the catheter to the laboratory. Table 1 compares the clinical characteristics of the cultured and noncultured catheters. There were no significant differences in both groups except for an increased rate of neutropenia (11.3% vs 2.4%; $P < .0015$), as well as an increased mortality (16.9% vs 5%; $P < .008$) in the noncultured group.

Table 1.—Characteristics of Cultured and Noncultured Catheters*

Characteristic	Cultured (n=340)	Noncultured (n=71)	P
Patient age, mo (mean ± SEM)	80.9 ± 3.6	68.8 ± 3.7	NS
Duration of insertion, h (mean ± SEM)	64.1 ± 4.1	66.9 ± 9.0	NS
Predisposing factors to infection, No. (%)			
Steroids	43 (12.7)	12 (16.9)	NS
OIA	35 (10.3)	12 (16.9)	NS
Neutropenia	8 (2.4)	8 (11.3)	<.0015†
Immune defect	2 (0.6)	0 (0)	NS
Percutaneous insertion, No. (%)	337 (99.1)	69 (97.2)	NS
Radial artery insertion site, No. (%)	294 (86.5)	63 (88.7)	NS
Use of antibiotics, No. (%)	281 (82.7)	61 (85.9)	NS
Local inflammation, No. (%)	13 (3.8)	1 (1.4)	NS
Reason for removal, No. (%)			
Malfunction	80 (23.5)	21 (29.6)	NS
Death	17 (5)	12 (16.9)	<.001†
Due to infection	3	2	NS
Without autopsy	5	6	NS

*OIA indicates other immunosuppressive therapy; NS, not significant.

†Significant ($P < .05$) by χ^2 test with Yates' correction.

The 340 cultured catheters were placed in 310 children aged 80.9 ± 3.6 months (range, 0.1 to 216 months) for a period of 64.1 ± 4.1 hours (range, 4 to 665 hours) (Table 1). The sex distribution was 62% (210/340) boys and 38% (130/340) girls. Most catheters (99%) were inserted percutaneously in a radial artery (86.5%); 78% (266/340) were placed in the operating room and 22% (74/340) in the PICU. Seventy-six percent (257/340) of the catheters were collected from surgical patients after major operations, 9% (32/340) from children with severe traumatic injuries, 8% (28/340) from medical patients with respiratory failure, and 7% (23/340) from children with other various medical diseases. No burned patients were studied. The end of medical indication was the reason for cannula removal in 66% of cases, followed by malfunction (24%), death (5%), and local ischemia (3%). Thirty-eight catheters (11%) were collected from patients with a culture-proved focus of infection unrelated to the catheter, such as pneumonia, epiglottitis, or pyelonephritis; 17 (46%) of these catheters were exposed to documented bacteremia. Eighty-three percent of the study population received systemic antibiotics during the time the catheter remained in place.

Cultures were negative in 92% (313/340) of the cultured cannulas (group 1). Five percent (17/340) were contaminated (group 2), and 3% (10/340) were considered either locally infected (eight) or associated with a possible catheter-related septicemia (two) (group 3, or infected group). No cases of CRS were identified.

There were no significant differences in patient characteristics between group 1 and group 2 with respect to age (80.0 ± 3.8 months vs 97.3 ± 15.8 months), duration of insertion (61.4 ± 4.1 hours vs 76.5 ± 21.5 hours), the presence of at least one predisposing factor to infection (15% vs

Table 2.—Characteristics of Catheters With Negative Cultures and of Catheters Associated With Local Infection (LINF) and Possible Catheter-Related Septicemia (PCRS)*

Characteristic	Negative (n=313)	LINF + PCRS (n=10)	P
Patient age, mo (mean ± SEM)	80.0 ± 3.8	80.2 ± 23.1	NS
Duration of insertion, h (mean ± SEM)	61.4 ± 4.1	125.4 ± 31.0	<.008†
Predisposing factors to infection, No. (%)	47 (15)	2 (20)	NS
Percutaneous insertion, No. (%)	311 (99.4)	9 (90.0)	NS
Location of insertion, No. (%)			
Operating room	245 (78.2)	6 (60.0)	NS
PICU	68 (21.8)	4 (40.0)	...
Site of insertion, No. (%)			
Radial	269 (85.9)	9 (90.0)	NS
Dorsalis pedis	30 (9.6)	1 (10.0)	...
Femoral	12 (3.9)	0 (0.0)	...
Brachial	2 (0.6)	0 (0.0)	...
Arterial line system, No. (%)			
System A	113 (36.1)	8 (80.0)	<.013‡
System B	200 (63.9)	2 (20.0)	...
Use of antibiotics, No. (%)	259 (82.8)	8 (80.0)	NS
Local inflammation, No. (%)	9 (2.9)	1 (10.0)	NS
Reason for removal, No. (%)			
End of medical indication	206 (65.8)	5 (50.0)	NS
Malfunction	73 (23.3)	2 (20.0)	NS
Death	16 (5.1)	1 (10.0)	NS

*NS indicates not significant; PICU, pediatric intensive care unit.

†Significant ($P < .05$) by two-tailed T test.

‡Significant ($P < .05$) by χ^2 test with Yates' correction.

24%), diagnosis on admission, site of insertion, percutaneous insertion, antibiotic use (83% vs 82%), or reason for removal. The only statistically significant difference was a lower incidence of local inflammation at the insertion site for negative catheters (3% vs 18%, $P = .012$). Eighteen microorganisms were recovered from the 17 contaminated cannulas, among which *Staphylococcus epidermidis* (four catheters), viridans *Streptococcus* (three catheters), *Staphylococcus capitis* (two catheters), and *Staphylococcus simulans* (two catheters).

Table 2 depicts the characteristics of catheters with negative cultures (group 1) compared with group 3 catheters. No significant difference was noted with respect to age, predisposing factors to infection, site of insertion, percutaneous insertion, use of antibiotics, and justification for removal. The incidence of local inflammation at the insertion site was not higher in group 3 catheters. Two factors were associated with an increased rate of catheter-related infection: type A system for arterial blood sampling and duration of insertion. Catheters with system A were not left in place for a longer period than cannulas with system B (63.2 ± 5.4 hours vs 65.9 ± 5.5 hours, $P = .76$).

The relationship between infection and duration of catheter placement is shown in Figs 2 through 4. Figure

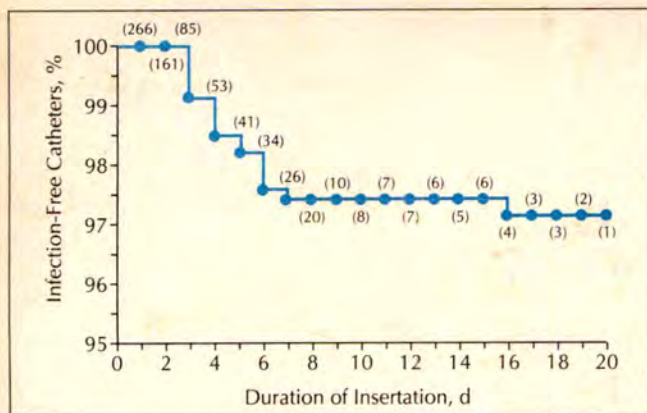


Fig 2.—Proportion of catheters free of infectious complications among the total group of 340 catheters. Percentages are expressed by cumulative survival analysis. Numbers in parentheses represent the numbers of cannulas still in place at the end of each interval.

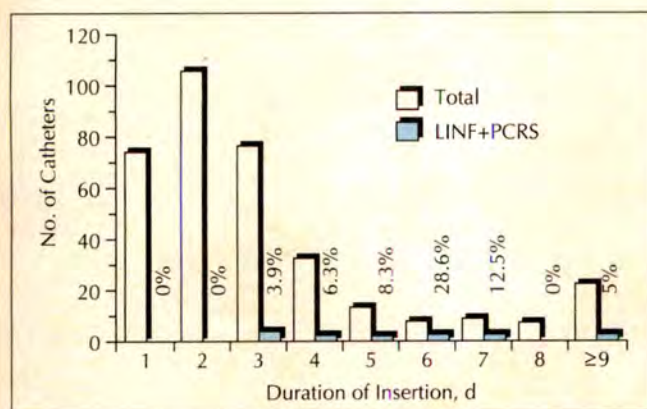


Fig 3.—Relationship of infection caused by arterial catheters to duration of catheter insertion. LINF indicates local infection of the catheter site; PCRS, possible catheter-related septicemia. Percentages indicate the proportions of catheters with LINF or PCRS vs the numbers of catheters removed.

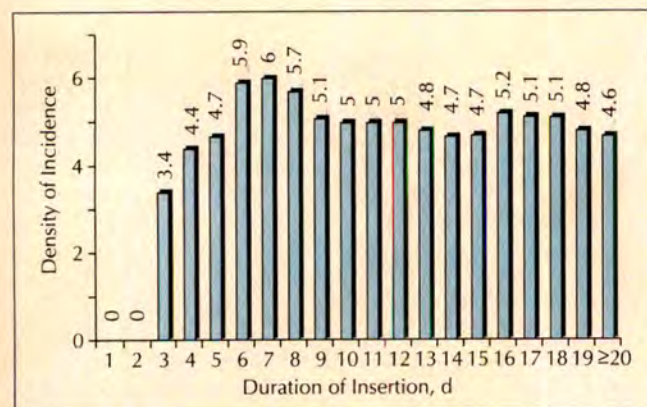


Fig 4.—Density of incidence of arterial catheter-related infectious complications. The daily probability of infectious complications per 10 000 hours of insertion is represented for days 1 through 20.

2 depicts the cumulative survival rate of catheters that remained free of infectious complications (ie, groups 1 and 2) from days 1 through 20. Most catheters (99.1% [337/340]) remained infection free even if left in place up to 72 hours, and 97.1% (330/340) were infection free even if in place for up to 20 days. No catheters became infected

within the first 2 days of insertion (Fig 3). After the first 48 hours, the risk of infection was 6.2% (10/161), with no precise correlation existing between duration of catheterization and infection; the incidence of infection increased after day 2 and then reached a plateau, with continued catheter use not being associated with significantly more infectious complications. The density of incidence of infectious complications describes the number of infections per 10 000 hours of insertion for each of days 1 through 20 (Fig 4). It is another representation of the same phenomenon: the density of incidence of infections increased from 3.4 per 10 000 hours of insertion on day 3 to 5.9 on day 6 and decreased to 4.6 thereafter.

Nine of the 10 infected catheters yielded *S epidermidis*, and one catheter yielded both *S epidermidis* and *S simulans*.

No contamination of infusate was detected in the 13 infusions sampled. Of the 18 catheters exposed to bacteremia or fungemia from unrelated sites of infection, not one was subsequently positive on SQ culture for the bloodstream pathogen. No case of septicemia due to contaminated infusate or of CRS from other infected sites was thus identified.

Six broth cultures were positive while the SQ culture remained negative. The organisms identified were *S epidermidis* (three cases), *Corynebacterium* species (one case), streptococcus MG intermedius (one case), and *Escherichia coli* (one case).

COMMENT

We had already shown in a previous report that the incidence of infection related to arterial catheterization in children is low⁵; indeed, not one of the 70 catheters studied was identified as being infected or as being the source of a CRS. Our present study confirms these preliminary results. It shows a 2.3% incidence of catheter-related local infection and a 0.6% incidence of possible CRS. This slightly higher incidence compared with our first study may simply be due to the larger sample (340 vs 70 cannulas). Furthermore, as the previous study took place during a much shorter period, its principal investigator (F.D.⁵) personally supervised the local disinfection of the skin at the catheterization site on catheter removal. Practically, this was not feasible for the present study, and a certain number of the so-called infected catheters may have actually become positive on withdrawal.

In adults, arterial catheters are a well-established source of nosocomial infection. The incidence of catheter-related infection and septicemia varies according to the study, ranging from 4% to 35% and from 0% to 5.4%, respectively.^{3,10-14} Our results show that the incidence of infection related to arterial catheterization in children is surely not higher than that in adults.

Many factors may contribute to the low incidence of infectious complications in this series, but these factors are not specific to the pediatric population. Less than 1% of the catheters were inserted by cutdown, which is associated with a higher risk of infection.³ No burned patients were studied, and these patients are more susceptible to catheter infection.¹² Furthermore, 87% of the catheters were inserted in the radial artery, which is an area of easy access, and only 11% were exposed to a focus of infection unrelated to the catheter.

The noncultured catheters and the criteria we used to diagnose infection also warrant discussion. It is unlikely that the loss of 71 catheters significantly biased the data. The patients in whom catheters were cultured were sim-

ilar to the group in whom the catheters were not cultured for all aspects but the mortality and the incidence of neutropenia, which were higher in the noncultured group. The higher mortality in the noncultured group may in itself explain why these catheters were not included; often, in these circumstances, the person who normally would have aseptically removed the catheter and sent it for culture had other priorities than culturing the catheter tip. The percentage of autopsies performed in the noncultured compared with the cultured group was similar (Table 1), as was the number of deaths due to infection (Table 1). The majority of deaths were not due to infection (Table 1), and infectious deaths were all caused by well-identified sources unrelated to the catheter. Furthermore, 77% (8/12) of deaths in the noncultured group occurred less than 48 hours after catheter insertion, rendering catheter-related infections most improbable in these patients. Among the four predisposing factors to infection recorded, neutropenia was the only one that occurred more frequently in the noncultured than the cultured group. Eight of the 71 noncultured catheters were placed in patients with neutropenia; it would be unlikely that more than one or two were infected, considering that all the catheters (eight) placed in patients with neutropenia and that were cultured were negative. We were, to our knowledge, the first group to publish the results of a prospective study on the incidence of arterial catheter-related infection and actually to compare cultured and noncultured groups.⁵ Surprisingly, many studies did not even consider the catheters lost during the study period,^{3,11,14,15} while some investigators only mentioned the lost catheters without taking them into consideration in their analyses.^{4,12,13,16}

There is no gold standard or unquestionable diagnostic criteria for catheter-related infection.¹³ This situation is attributable to two factors: the pathogenesis of intravascular catheter infection is multifactorial and the diagnostic tools are imperfect. The majority of infections are due to organism multiplication at the insertion site, with subsequent multiplication around the catheter in the subcutaneous space and then the bloodstream.⁶ Other mechanisms leading to catheter sepsis are infusate contamination, hematogenous seeding of the catheter tip, and hub contamination.¹² To obviate false-negative results, each of these mechanisms should theoretically be considered, with the inherent risk of infection overdiagnosis.

We took into account the first three of these mechanisms in our study. We did not culture the internal surface of the catheter hub^{17,18}; catheter hub cultures are still not routinely used to diagnose arterial catheter-related infection,^{13,15} and false-positive hub cultures have been reported.¹² Our criteria for diagnosing catheter-related infection were based on SQ culture, and they were rather stringent. We used 10 CFUs on SQ culture as the cutoff point for diagnosing infection, instead of 15 CFUs as proposed by Maki et al,⁶ with the risk of false-positive results that this implies. The 10-CFU cutoff point was adopted because, with pediatric catheters, only the distal 2 cm of the arterial catheter was available for culture, as opposed to the distal 5.7 cm in the study by Maki et al.⁶ We did not use 5 CFUs, as suggested by Collignon et al,¹⁹ because this only increases the number of false-positive results and probably offers no substantial advantage in terms of diagnosing bacteremia.^{17,20} Because even a minute bacterial inoculum from skin flora can give a falsely positive broth culture,¹⁸ we did not consider as significant a positive broth culture in the face of a negative SQ culture. We did not perform quantitative cultures of the tip of the catheters be-

cause this technique had not been validated in our laboratory. Cleri et al²¹ recently proposed that this method, by taking into account the culture of the internal surface, is more precise and eliminates the false-negative results that can be obtained with the SQ culture. Nonetheless, the experience with this technique is still limited.

One may argue that the almost universal use of antibiotics in our patients, either prophylactically or as therapeutic agents, may have aborted CRSs, the catheters being falsely negative on removal. The same argument could be advocated for every study using positive SQ or quantitative cultures, instead of clinical criteria, to diagnose catheter-related infection.^{11-13,15} In our series, only 18 catheters (5%) were exposed to documented bacteremia during their insertion. In 14, the positive blood culture was obtained less than 6 hours after catheter insertion, rendering the diagnosis of CRS very unlikely. In three cannulas among the four others, a source of infection unrelated to the catheter was identified. In only one case, no focus of infection except the catheter itself could be found to explain the bacteremia: the blood culture was sampled through a subclavian line 51 hours after insertion of the arterial catheter and yielded *S. simulans*. The arterial catheter was removed 3 days after this sampling and was sterile. This isolated case could have been a false-negative CRS, but this is very unlikely considering (1) the short interval between catheter insertion and blood culture sampling (51 hours) and (2) the fact that this blood culture was done through a central venous line that was very possibly contaminated itself, but was not cultured because of accidental removal. Taking into account the limits of the criteria we used to diagnose catheter-related infections (see above), we are convinced that the very low incidence of infection reported is real.

In our study, two factors were associated with an increased rate of possible catheter-related infection: type A system for arterial blood sampling and the duration of insertion.

The major differences between systems A and B for arterial blood sampling were the following: (1) system A has 120 cm of pressure tubing through which blood is drawn back to clear the line of heparin before sampling, whereas system B has a one-way valve that does not allow blood backflow into the tubing; (2) a stopcock in system A facilitates blood sampling; and (3) the blood sampling procedure with system B necessitated more manipulations than system A. Obviously, the present study was not designed to analyze this question specifically. Nonetheless, considering that stopcocks are probably one of the sources of catheter-related infections²² and that system A as used in our unit is by far the most widely used in North America for arterial blood sampling, a prospective study focusing on this aspect of catheter maintenance appears warranted.

The duration of cannulation, as a factor influencing the incidence of colonization (or local infection of the catheter site), has been studied by many investigators; the majority found that duration did increase the risk of colonization,^{3,11,16,23} while others concluded the contrary.^{13,14} In this study, the risk of infection and duration of catheter placement were related, but in a peculiar way. The risk of infection was nonexistent for the first 48 hours of catheter placement. After that period, it was 6.2% but correlated poorly with duration of insertion, ie, it did not increase in proportion with duration. The density of incidence of infectious complications is another way to represent the same observation. It shows two different phases: a first phase of zero risk lasting 48 hours followed

by a second phase, characterized by a nonsignificantly fluctuating infectious risk up to day 20. This phenomenon has been described, although not discussed, by almost all investigators who have so far studied arterial catheter-related infections in adults with systematic cultures^{3,11,13,23}, the "no-risk" period varies between 24^{3,11} and 48^{13,23} hours, and during the second phase, the risk of local and systemic infection increases severalfold but, again, not significantly from day to day.

These observations surely allow us to hypothesize that the zero-risk period corresponds to an incubation phase after which infection may happen; they are in agreement with the multifactorial pathogenesis of catheter-related infection discussed above. Indeed, the density of incidence of infections over time observed in this study is almost unexplainable by a single mechanism. As already mentioned, organism multiplication at the insertion site is possibly the major mechanism leading to infection. The fact that the density of the incidence of infectious complications did not vary significantly after the first 48 hours of insertion might indicate that spread of organisms down the transcutaneous tract may begin at any time after insertion, with the risk factors still to be determined; if this organism multiplication was mostly determined by the procedure of insertion itself, nosocomial infections should have decreased significantly after day 3 to 4, and clearly this was not the case. If contamination of the infusate or hematogenous seeding of the catheter site was the most important factor leading to infection, the density of the incidence of infectious complications should have increased proportionately with duration of insertion, and, here again, this was not the case. All these mechanisms could be causative factors, acting in sequence at different periods during insertion.

Routine replacement of the tubing and continuous flow device every 48 hours and of the infusion fluid and dressing every 24 hours is recommended by the Centers for Disease Control (Atlanta, Ga).²⁴ We had already questioned the merits of these recommendations.⁵ The results reported here reinforce our opinion. Considering the very low rate of infection reported without these routine replacements, the significant costs involved, and the fact that minimum manipulation of the system may decrease the risk of unwanted contamination of both infusate and insertion site,^{14,16} we still consider routine changes of tubing, infusion fluid, and continuous flow device debatable. Less frequent changes of the monitoring system have not been prospectively studied so far, and this should be done, particularly for financial reasons.

More than 10 years ago, Band and Maki³ recommended systematic replacement of arterial catheters every 4 days in adults. According to our results, this replacement should be done every 48 hours, instead of every 4 days, to be fully effective in minimizing the infection risk. Indeed, this would be the ideal arterial catheter policy. Exchanging the catheters over a guidewire could be another alternative in preventing nosocomial infections.¹⁵ However, considering (1) the low rate of infection demonstrated here (not a single case of proved CRS was identified); (2) the fact that, after the first 48 hours, the density of the incidence of infectious complications did not increase with time; (3) the much greater technical difficulties of replacing or exchanging catheters in children; and (4) the suffering incurred by such manipulations, we strongly suggest that arterial catheters should not be replaced routinely in children.

This study would not have been possible without the invaluable help of the nursing staff of St-Justine Hospital PICU. We thank Nancy Haley, MD, for reviewing the manuscript.

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Brief Summary

INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with bronchial asthma.

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium. No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reactions attributed to cromolyn sodium treatment were:

- Throat irritation or dryness
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- Cough
- Wheeze
- Nausea

The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm (sometimes severe, associated with a precipitous fall in pulmonary function (FEV₁), cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy.

The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarthritis vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

CAUTION: Federal law prohibits dispensing without prescription.

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Radiological Case of the Month

George P. Giacola, MD (Contributor), Beverly P. Wood, MD (Section Editor)

A 2050-g newborn of 36 weeks' gestation was born by vaginal vertex delivery with low forceps assistance after 16 hours of labor. The newborn's Apgar scores were 4 and 8 at 1 and 5 minutes, respectively. The mother, a 14-year-old girl, had received no prenatal care. The infant

forcefully vomited the first formula feeding, given at age 12 hours.

Results of physical examination showed the newborn to be active and in no distress. The newborn's length was 49 cm, and the head circumference, 35 cm. An extensive left parietal cephalohematoma was present. The white blood cell count was $14.9 \times 10^9/L$, and the differential count was as follows: neutrophils, 53%; lymphocytes, 37%; and monocytes, 10%. The hemoglobin value was 120 g/L, and the bilirubin value was 128 $\mu\text{mol/L}$.

Because of continued vomiting and regurgitation of feedings, a frontal roentgenogram of the abdomen was obtained after insertion of a nasogastric tube (Figs 1 and 2).

Accepted for publication June 19, 1991.

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Figure 1.



Figure 2.

Denouement and Discussion

Congenital Syphilis

Fig 1.—Symmetric radiolucent metaphyseal bands involve the femora and ilia. Periosteal new bone is present along the shafts of the long bones (results of VDRL test, 1:32; results of a fluorescent treponemal antibody absorption test were positive).

Fig 2.—Roentgenogram of legs showing periosteal new bone and Wimberger's sign (arrow).

Congenital syphilis is an important perinatal complication that has recently increased substantially in occurrence.¹ The roentgenographic characteristics of congenital syphilis usually precede clinical manifestations and may identify the condition when results of conventional serologic tests are inconclusive.² In a small number of affected neonates, florid clinical signs and abnormal results of serologic tests occur without demonstrable skeletal abnormality. Characteristically, diffuse bony involvement affecting the metaphyses and diaphyses is present.³ The metaphyseal lesions appear as irregular bands of diminished mineralization or focal circumscribed areas of metaphyseal and cortical bone destruction. Disruption in the orderly progression of calcification of cartilaginous osteoid to normal bone is evidenced as transverse lucent bands at the metaphyseal ends with or without an adjacent band of sclerosis. Destructive metaphysitis takes several forms. Focal erosion of the semilunar notch of the ulna denotes congenital luetic infection. Destruction of the medial aspect of the proximal tibial metaphysis (Wimberger's sign) is characteristic but not pathognomonic of congenital syphilis. Wimberger's sign also occurs in osteomyelitis, hyperparathyroidism, and infantile generalized fibromatosis.⁴ Longitudinal metaphyseal

bands of decreased density, "celery stalks," occur in syphilis, congenital rubella syndrome, cytomegalovirus infection, and other viral transplacental infections.⁵ Subperiosteal inflammation in the diaphysis produces cortical destruction and periosteal elevation in single or multiple layers, with new bone formation along the length of the diaphysis. Polyostotic, symmetric bone involvement is characteristic of congenital syphilis.⁶ The long bones, pelvis, vertebrae, and small tubular bones are all susceptible to involvement. Lytic lesions of the crania mimic those of Langerhans' cell histiocytosis. A delay of approximately 5 weeks between initial infection of the fetus and radiologic evidence of osteitis is typical, with periostitis occurring later.⁷ The pathogenesis of bone changes is focal inflammation produced directly by spirochetal infection or dystrophic alteration in endochondral bone formation secondary to generalized sepsis.

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Picture of the Month

Luis A. Vera, MD; Nayere Zaeri, MD; Hallam Hurt, MD (Contributors);
Murray Feingold, MD (Editor for This Case); Walter W. Tunnessen, Jr, MD (Section Editor)



Figure 1.



Figure 2.

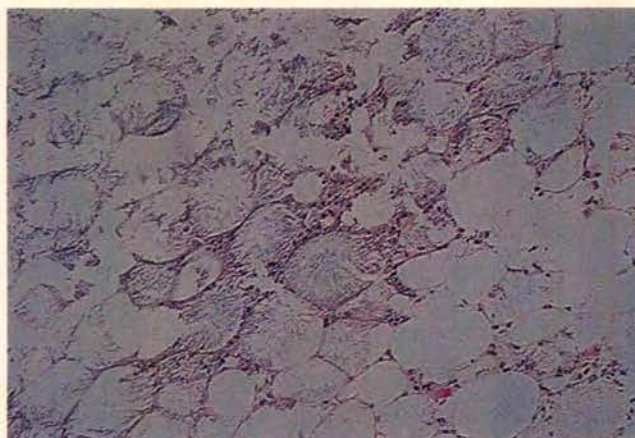


Figure 3.

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Tunnessen (Picture of the Month), The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104, or Dr Wood (Radiological Case of the Month), Department of Radiology, Children's Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Accepted for publication January 10, 1991.
Contributed from the Division of Neonatology, Albert Einstein Medical Center, Philadelphia, Pa.

Reprint requests to National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Subcutaneous Fat Necrosis of the Newborn

Fig 1.—At initial presentation, skin is taut, erythematous, and indurated.

Fig 2.—In 24 to 28 hours, the skin acquires a purple hue.

Fig 3.—Results of biopsy of the involved skin show the characteristic fat cell necrosis with central needle-shaped crystal formation in the fat cells.

Manifestations

Subcutaneous fat necrosis of the newborn is a benign condition of unknown origin affecting the subcutaneous fat tissue in the first weeks of life. It is characterized clinically by multiple subcutaneous, indurated, erythematous plaques and nodules that are neither tender nor warm to palpation. The condition begins as an area of edema at the affected sites and rapidly progresses to variably circumscribed, confluent, red lesions that change to a purple hue in several days. The skin appears taut and shiny. The lesions may become fluctuant, and spontaneous drainage of necrotic fat may occur. Areas of the body most commonly involved are the buttocks, back, arms, thighs, legs, and shoulders.

Results of histologic examination of the condition typically include necrosis of subcutaneous fat with needle-shaped crystal formation in the fat cells. Calcium deposits are sometimes seen

in the central part of the degenerating fat cells. The epidermis and dermis appear normal on microscopic examination.

Many factors have been implicated as causes of this condition, with the most likely being hypothermia, obstetric trauma, and perinatal asphyxia. Hypercalcemia and thrombocytopenia have been observed in several cases; however, in general, laboratory findings are nonspecific and, in most cases, within normal limits.

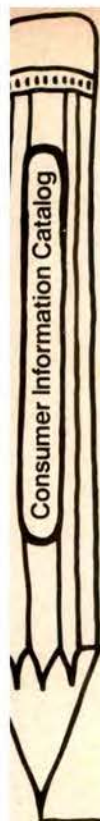
Differential diagnosis should include cellulitis and sclerema neonatorum. Sclerema neonatorum is very often confused with subcutaneous fat necrosis of the newborn; however, it is characterized by diffuse hardening of the skin, and is often associated with sepsis. The prognosis of sclerema neonatorum is grave.

Treatment

Treatment of subcutaneous fat necrosis is symptomatic, and should concentrate on other concurrent illnesses such as sepsis. Prognosis is good, with gradual resolution of the lesions in a few months. Residual cosmetic problems may arise from subcutaneous fat atrophy, but these may be corrected with plastic surgery.

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WARNINGS: Risk of GI Ulcerations, Bleeding, and Perforation with NSAID Therapy: Physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months' to two years' duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, no risk factors have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population.

PRECAUTIONS: General: Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding.

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints the drug should be discontinued and the patient should have an ophthalmologic examination.

Fluid retention and edema have been reported with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

Ibuprofen can inhibit platelet aggregation and prolong bleeding time. CHILDREN'S ADVIL® SUSPENSION should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

The antipyretic and anti-inflammatory activity of ibuprofen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Small decreases (usually not exceeding one gram) in hemoglobin and hematocrit with an apparent dose response relationship have been observed following chronic administration. If there are no signs of bleeding, it is probably not clinically important.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have their therapy tapered slowly when CHILDREN'S ADVIL® SUSPENSION is added to the treatment program.

Aspirin: Aspirin may cause bleeding with fever and coma has been observed on rare occasions in adult patients on ibuprofen therapy. Although it is more likely to occur in patients with systemic lupus erythematosus and related connective tissue diseases, it has been reported in adult patients who do not have underlying chronic disease. If signs or symptoms of meningitis develop in a patient on CHILDREN'S ADVIL® SUSPENSION, the possibility of its being related to ibuprofen should be considered.

Renal Effects: As with other nonsteroidal anti-inflammatory drugs, long-term administration of ibuprofen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with preexisting conditions leading to reduction in renal blood flow or blood volume. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose dependent reduction in prostaglandin formation and precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, and those taking diuretics and the elderly. Those patients at high risk who chronically take CHILDREN'S ADVIL® SUSPENSION should have renal function monitored if they have signs or symptoms of azotemia. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation.

Information for Patients: Physicians may wish to discuss with their patients the potential risks and likely benefits of treatment with CHILDREN'S ADVIL® SUSPENSION.

Laboratory Tests: Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with ibuprofen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur, CHILDREN'S ADVIL® SUSPENSION should be discontinued.

Diabetes: Each 5 mL of CHILDREN'S ADVIL® SUSPENSION contains 2.5 g of sucrose which should be taken into consideration when treating patients with impaired glucose tolerance. It also contains 350 mg of sorbitol per 5 mL. Although in clinical trials CHILDREN'S ADVIL® SUSPENSION was not associated with more diarrhea than control treatments, should a patient develop diarrhea, the physician may wish to review the patient's dietary intake of sorbitol from other sources.

Drug Interactions: Coumarin-type Anticoagulants: Bleeding has been reported when ibuprofen and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants; the physician should be cautious when administering CHILDREN'S ADVIL® SUSPENSION to patients on anticoagulants.

Aspirin: Concurrent use of aspirin is not recommended.

Methotrexate: In vitro studies indicate that ibuprofen could enhance the toxicity of methotrexate. Caution should be used if CHILDREN'S ADVIL® SUSPENSION is administered concomitantly with methotrexate.

H₂ Antagonists: In studies with human volunteers, coadministration of cimetidine or ranitidine with ibuprofen had no substantive effect on ibuprofen serum concentrations.

Furosemide: Ibuprofen can reduce the natriuretic effect of furosemide and thiazides in some patients. During concomitant therapy with CHILDREN'S ADVIL® SUSPENSION, the patient should be observed closely for signs of renal failure as well as to assure diuretic efficacy.

Lithium: Ibuprofen produced an elevation of plasma lithium levels (15%) and a reduction in renal lithium clearance (19%) in a study of 11 normal volunteers during the period of concomitant drug administration. Patients should be observed carefully for signs of lithium toxicity. Read package insert for lithium before its use.

Pregnancy: Administration of ibuprofen is not recommended during pregnancy or for use by nursing mothers.

Infants: Safety and efficacy of CHILDREN'S ADVIL® SUSPENSION in children below the age of 12 months have not been established.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with CHILDREN'S ADVIL® SUSPENSION is gastrointestinal. In clinical trials among adults involving chronic administration of ibuprofen, the percentage of patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Incidence Greater Than 1% (but less than 3%), Probable Causal Relationship (see PRECAUTIONS): Abdominal cramps or pain, abdominal distress, constipation, diarrhea, epigastric pain, fullness of the GI tract (bloating and flatulence), heartburn, indigestion, nausea, vomiting, dizziness, headache, nervousness, pruritus, rash (including maculopapular type), tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation).

Precise Incidence Unknown (but less than 1%), Probable Causal Relationship (see PRECAUTIONS): Abnormal liver function tests, gastric or duodenal ulcer with bleeding and/or perforation, gastritis, gastrointestinal hemorrhage, hepatitis, jaundice, melena, pancreatitis, alopecia, erythema multiforme, Stevens-Johnson syndrome, urticaria, vesiculobullous eruptions, aseptic meningitis with fever and coma, confusion, depression, emotional lability, insomnia, somnolence, amblyopia (blurred and/or diminished vision, scotomata and/or changes in color vision), hearing loss, agranulocytosis, aplastic anemia, decreases in hemoglobin and hematocrit, eosinophilia, hemolytic anemia (sometimes Coombs' positive), neutropenia, thrombocytopenia with or without purpura, congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations, anaphylaxis, bronchospasm (see CONTRAINDICATIONS), syndrome of abdominal pain, fever, chills, nausea and vomiting; acute renal failure in patients with pre-existing significantly impaired renal function, azotemia, cystitis, decreased creatinine clearance, hematuria, polyuria, dry eyes and mouth, gingival ulcers, rhinitis.

Precise Incidence Unknown (but less than 1%), Causal Relationship Unknown: Dream abnormalities, hallucinations, paresthesias, pseudotumor cerebri, phototoxic skin reactions, toxic epidermal necrolysis, cataracts, conjunctivitis, diplopia, optic neuritis, bleeding episodes (e.g., epistaxis, menorrhagia), acidosis, gynecomastia, hypoglycemic reactions, arrhythmias (sinus tachycardia, sinus bradycardia), angioedema, Henoch-Schönlein vasculitis, lupus erythematosus syndrome, serum sickness, renal papillary necrosis.

*Reactions occurring in 3% to 9% of adult patients treated with ibuprofen.

OVERDOSAGE: Patients with a history of ingestion of greater than 100 mg/kg should have induced emesis or gastric lavage. Multiple dose oral administration of activated charcoal may be useful. Supportive therapy may include oxygen, respiratory support, and parenteral fluids. Because the drug is acidic and excreted in the urine, administration of sodium bicarbonate and induction of diuresis may be beneficial.

DOSEAGE AND ADMINISTRATION: Fever: 5 mg/kg if baseline temperature is 102.5°F or below or 10 mg/kg if baseline temperature is greater than 102.5°F, every 6-8 hours (children); 400 mg every 4-6 hours (adults).

Mild to moderate pain in adults: 400 mg every 4 to 6 hours.

Juvenile Arthritis: 30-40 mg/kg day in 3 or 4 divided doses.

RA and OA: 1200-3200 mg per day in 3 or 4 divided doses.

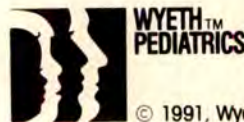
Dysmenorrhea: 400 mg every 4 hours.

HOW SUPPLIED: 4 and 16 oz. bottles

Caution: Federal law prohibits dispensing without prescription.

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A Variant Form of Thrombasthenia

Michael D. Tarantino, MD; James J. Corrigan, Jr, MD; Lewis Glasser, MD;
Claire M. Payne, PhD; Monette A. Jeter, PhD

• We encountered two siblings with abnormal bruising since infancy. Studies revealed functional platelet defects characterized by a lack of platelet aggregation and adenosine triphosphate release on exposure to adenosine diphosphate and collagen as well as variable responses with ristocetin (at concentrations of ≤ 1.25 g/L) and arachidonic acid. In addition, little or no platelet aggregation was observed after exposure to hexadimethrine bromide (Polybrene), the calcium ionophore A23187, and the thromboxane/endoperoxide analogue U46619. The membrane proteins IIIa and Ib were present, as determined with monoclonal antibody testing, and no platelet-associated IgG was found. Platelet analysis with routine electron microscopy and ultrastructural cytochemistry revealed normal morphologic features and no deficiencies in the number of alpha granules dense bodies and other organelles. The platelet abnormality may represent a new variant of thrombasthenia.

(AJDC. 1991;145:1053-1057)

Congenital or inherited abnormalities in the function of blood platelets produce a clinical bleeding picture similar to quantitative defects (thrombocytopenia), ie, mucus membrane and skin petechiae, ecchymoses, and the immediate onset of bleeding with trauma. The congenital defects have been classified into disorders of platelet adhesion (eg, von Willebrand disease and Bernard-Soulier syndrome), primary aggregation (eg, thrombasthenia), secretion (eg, storage pool disease and release defects), and procoagulant activities (eg, platelet factor 3 deficiency).¹

Glanzmann thrombasthenia is an autosomal recessive disorder characterized by a deficiency or an abnormality of the platelet membrane glycoprotein IIb-IIIa complex. Patients with this disorder have a normal platelet count, normal platelet morphologic features, prolonged bleeding time, absent or substantially reduced platelet aggregation by adenosine diphosphate (ADP) and other agonists, nor-

mal platelet aggregation (agglutination) in response to ristocetin, and normal results of plasma coagulation studies. Clot retraction may or may not be impaired.²⁻⁵

The patient described herein had the usual laboratory findings of thrombasthenia, but his platelets also reacted poorly to ristocetin, and GP IIIa and GP Ib were detected in his platelets. His sister had similar findings. We report this unusual variant of thrombasthenia.

PATIENT REPORTS

A 7-year-old Mexican boy had excessive skin bruising, prolonged bleeding with skin lacerations, and frequent epistaxis since the age of 1 year. There was no history of joint pain or swelling. The patient took no medications, and his growth and development were normal.

The physical examination revealed normal findings, except for the skin findings. Examination of the skin revealed scattered ecchymoses, the largest of which was 3 cm in diameter. Petechiae were noted over the patella, elbows, and sternum.

Laboratory studies revealed normal red blood cell, white blood cell, and platelet counts. Prothrombin and partial thromboplastin times were within the normal range. The bleeding time was greater than 20 minutes on three separate occasions.

At the initial evaluation, the patient was treated empirically with oral prednisone (1 mg/kg of body weight per day). After 1 month, the studies were repeated, and the results revealed no change. The bleeding time remained prolonged, and the platelet count remained normal.

The boy's 3-year-old sister was also noted to have excessive skin bruising and prolonged bleeding after skin lacerations since the age of 1 year. Likewise, she had no joint symptoms and took no medications.

The family history revealed that the biologic father of the children also suffered from skin bruising since childhood and had experienced prolonged bleeding after shaving cuts. The father has three half-sisters who do not experience these symptoms but also has two brothers who have skin bruising. The paternal grandfather also has a history of excessive skin bruising. The family history revealed no consanguinity. However, the coagulation and platelet studies yielded normal findings in the father and mother (see the "Results" section).

MATERIALS AND METHODS

Initial Tests

A complete blood cell count, platelet count, prothrombin time, activated partial thromboplastin time, and template bleeding time were determined with use of standard methods in each case. Plasma von Willebrand antigen and activity and factor VIII activity were measured in the index case.⁶⁻⁸ Platelet-associated immunoglobulin was determined by the method of Finley et al.⁹

Accepted for publication February 19, 1991.

From the Departments of Pediatrics (Drs Tarantino, Corrigan, and Jeter) and Pathology (Drs Glasser and Payne) and The Children's Research Center, The University of Arizona Health Sciences Center, Tucson. Dr Corrigan is now with Tulane University School of Medicine, New Orleans, La. Dr Tarantino is now with the University of Wisconsin Medical School, Madison.

Reprint requests to Tulane University School of Medicine, 1430 Tulane Ave, New Orleans, LA 70112 (Dr Corrigan).

Platelet Aggregation and Adenosine Triphosphate (ATP) Release

Blood was collected by venipuncture into plastic tubes containing 3.8% sodium citrate. The ratio of blood to anticoagulant was 9:1. Platelet-rich plasma (PRP) was obtained by centrifugation of the blood at 180g for 10 minutes at room temperature. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 1500g for 10 minutes. The concentration of platelets in the PRP platelet count was adjusted to approximately $250 \times 10^9/L$ for all tests. A lumiaggregometer was used to measure platelet aggregation and ATP secretion (Chrono-log Corp, Havertown, Pa).¹⁰ Adenosine triphosphate-generated chemiluminescence was measured with firefly luciferase-luciferin (Chronolume, Chrono-log Corp).¹¹ The reaction mixture contained 0.4 mL of PRP and 0.1 mL of agonist. The agonists used (and their final concentration in the reaction mixture) were as follows: ADP (4.6, 23, and 46 $\mu\text{mol/L}$; Sigma Chemical Co, St Louis, Mo), collagen (Sigma Chemical Co), arachidonic acid (5.0 and 7.0 mmol/L , Chrono-log Corp), ristocetin (1.25, 1.0, 0.5 g/L ; Pacific Hemostasis Laboratories, Ventura, Calif), calcium ionophore A23187 (19 $\mu\text{mol/L}$; Sigma Chemical Co), thromboxane/endoperoxide analogue U46619 (0.5 $\mu\text{mol/L}$; Caymer Chemicals, Ann Arbor, Mich), hexadimethrine bromide (Polybrene), (1 g/L ; Abbott Laboratories, Chicago, Ill), snake venom (*Crotalus atrox*, 1 g/L).

Platelet Glycoprotein Antigens

Glycoprotein Ib and IIIa were analyzed by flow cytometry.⁹ Mouse monoclonal antihuman platelet glycoprotein Ib and IIIa antibodies were obtained from Dako Corp, Santa Barbara, Calif. Platelets were washed, resuspended, and analyzed with the Epics V (Coulter Electronics Inc, Hialeah, Fla). Mouse antihuman platelet glycoprotein was added to the normal control and to the patient's platelet suspension and incubated for 30 minutes at 22°C. After washing, fluorescein isothiocyanate-conjugated goat antimouse IgG was added and incubated for 30 minutes in the dark at 22°C. A positive reaction was measured using the log of green fluorescence.

Ristocetin Cofactor

Ristocetin cofactor was measured in platelet-poor plasma by the method of Allain et al.⁸ Briefly, 0.05 mL of a 1:2 dilution of plasma was added to a 0.40-mL suspension of lyophilized platelets (Helena Laboratories, Beaumont, Tex) and 0.05 mL of ristocetin. Platelet aggregation was measured with an aggregometer (Chrono-log Corp). The maximum slope of the aggregation curve was calculated, and the activity of the patient's ristocetin cofactor was determined.

Electron Microscopy

One milliliter of blood from the patient and each control was spun in a Wintrobe tube at 2500 rpm for 10 minutes in a swinging bucket clinical centrifuge (Beckman TJ-6, Beckman Instruments Inc, Fullerton, Calif). The plasma was removed, and the buffy coat was fixed in situ with 3% glutaraldehyde in 0.1 mol/L of phosphate buffer (pH 7.3). One-millimeter slices of the buffy coat plug were prepared, postfixed for 1 hour in 1% osmium tetroxide, dehydrated in a graded series of ethanols, and embedded in Spurr's epoxy resin. One-micron sections were prepared, stained with toluidine blue O, and examined for proper orientation of the platelet layer. Ultrathin sections were prepared with an ultramicrotome (Dupont-Sorvall MT-5000, Dupont-Sorvall, Boston, Mass) and counterstained with uranyl acetate-lead citrate before examination under an electron microscope (JEOL 100 CX, JEOL USA Inc, Peabody, Mass).

Ultrastructural Cytochemical Reactions.—Three different platelet preparations were prepared (with only plastic tubing and plastic tubes) for the following three cytochemical reactions that stain different components of the dense bodies: uranaffin reaction stains the nucleotides (ADP/ATP),¹²⁻¹⁴ the chromaffin reac-

Table 1.—Preliminary Studies

Variable	Patient	Normal Control
Platelet count, $\times 10^9/L$	351	150-350
Platelet morphologic features	Normal	Normal
Prothrombin time, s	11.5	10.7-12.3
Partial thromboplastin time, s	29.1	25.8-35.2
Fibrinogen, g/L	3.07	1.5-3.5
Bleeding time, min	>20	1-10.5
Euglobulin lysis time, h	>2.0	>2.0
Ristocetin cofactor assay, % of normal	77	44-160
Factor VIII activity, U/dL	63	50-150
von Willebrand factor antigen, % of normal	68	60-150
Clot retraction	Fair	Good to excellent

Table 2.—Platelet Aggregation and Adenosine Triphosphate Release

Reagent	Aggregation, %		ATP Release, $\mu\text{mol/L}$	
	Patient	Normal Range	Patient	Normal Range
ADP, $\mu\text{mol/L}^*$				
4.6	0	47-74	0.07	0.18-2.7
23	0	>60	0.17	0.18-2.7
46	0	100	>3.35	>3.35
Collagen	0	42-70	0.03	0.5-2.1
Arachidonic acid, mmol/L				
2.5	0	35-80	0.30	0.07-1.3
5.0	32	>50	0.39	0.18-2.0
Thrombin, 1.0 U/mL	0	>70	1.09	>0.5
Ristocetin, g/L				
1.5	62	>80
1.25	52	>54
	0
	42
1.0	30	54-75
	0

*ADP indicates adenosine diphosphate.

tion¹⁵ stains the amines (serotonin or 5-hydroxytryptamine), and Weiss' fixation¹⁶ procedure (contains 2.25 mmol/L of calcium chloride) with postossification allows the visualization of the calcium ions.

Quantitation of Platelet Dense Bodies.—All platelets were evaluated for reactive sites with the use of grids that were not counterstained with uranyl acetate-lead citrate. The platelets were viewed and scored at a microscopic magnification of $\times 10,000$; the number of reactive sites in each of 100 consecutive platelet profiles were determined. A reactive site was defined as

Table 3.—Quantitation of Platelet-Dense Bodies by Electron Microscopy*

Subject	Cytochemical Stain		
	Ca ⁺⁺	Nucleotides†	Amines (Serotonin)§
Patient	1.47	0.84	0.33
10-year-old male control	1.05	0.64	0.45
8-year-old female control	0.73	0.57	0.23
Adult male			
1	0.30	0.51	0.36
2	0.82	0.81	0.53
Adult female	0.72	0.64	0.29

*Values are number of reactive sites per platelet profile (100 platelet profiles were examined).

† Weiss' fixative.

‡ Uraffin reaction.

§ Chromaffin reaction.

any electron-dense precipitate that was visually more electron dense than the surrounding noncounterstained platelet organelles. These reactive sites had either a solid, punctate, or crystalline appearance. In the case of the uraffin reaction, a platelet dense body was also scored as positive if the granule membrane alone was stained; this membrane staining was only seen with the uraffin reaction.¹³

RESULTS

Initial Test Results

All of the results (Table 1) were noted to be in the normal range, except for the bleeding time, which was greater than 20 minutes. The bleeding time was remeasured 1 month later, and the same result was obtained. Bleeding times of the patient's mother and father were noted to be 4.5 and 6 minutes, respectively. The bleeding time was not determined for the patient's sister. The platelet-associated immunoglobulin test result was negative in the patient. The paternal uncles and paternal grandfather were not available for testing. As noted, the patient's plasma level of factor VIII activity, von Willebrand factor protein, and von Willebrand factor activity (ristocetin cofactor) were normal.

Platelet Aggregation and ATP Release

The degree of platelet aggregation to various agents is shown in Table 2. No aggregation was seen in the patient's platelets when exposed to either increasing concentrations of ADP or with collagen. Arachidonic acid at 5.0 mmol/L induced minimal aggregation (32%). The response to ristocetin showed an inconsistent pattern, being 0% and 42% with the use of 1.25 g/L of the antibiotic.

Aggregation studies with other agonists showed no response with thrombin (1 U/mL), A23187 (a calcium ionophore), and U46619 (a thromboxane/endoperoxide analogue) and only a 15% response with 1.0 g/L polybrene (normal control, 75%).^{17,18} *Crotalus atrox* venom, however, caused 100% clumping.¹⁹ The release of ATP was evident with 46 μmol/L of ADP and with thrombin (1.0 U/mL).

Aggregation and ATP release studies performed in the 3-year-old sister revealed no aggregation on exposure of PRP to ADP (4.6 μmol/L), collagen, and epinephrine. However, platelet aggregation was noted after the addi-

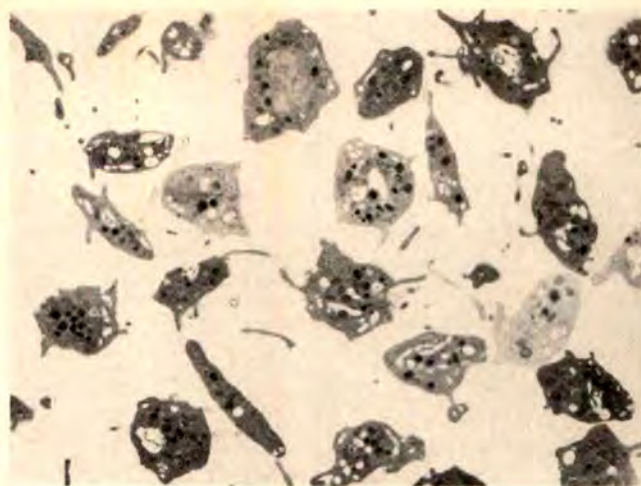


Fig 1.—Low-power electron micrograph of platelet profiles obtained from patient with abnormal bruising and defective platelet aggregation. Platelets are of normal size and show no deficiencies of organelles. Some of the platelets have a discoid shape and others exhibit pseudopodal extensions, the latter of which is indicative of platelet activation (uranyl acetate-lead citrate, original magnification × 8700).

tion to ristocetin, ranging from 7% aggregation in a 0.5-g/L solution to 51% aggregation in a 1.25-g/L solution of ristocetin. Release of ATP was not observed when the sister's platelets were exposed to epinephrine, ADP, or collagen.

Studies of platelet aggregation and ATP release in PRP from the parents revealed normal aggregation with collagen, ristocetin (1.25 g/L), arachidonic acid (5 mmol/L), and ADP (23 μmol/L).

Platelet Antigens

Platelets from the index case fluoresced after incubation with monoclonal antibodies against both platelet glycoproteins Ib and IIIa, indicating the presence of these glycoproteins in the platelet membrane. These tests were not performed on other family members.

Electron Microscopic Findings

Examination of the patient's platelets with transmission electron microscopy revealed a normal content and complement of organelles²⁰ (Fig 1). Compare the patient's platelets (Fig 1) with those of an age-matched control (Fig 2). Alpha granules were present and were of normal size and shape. Quantitative cytochemical studies with the use of Weiss' fixative (Fig 3) and the uraffin and chromaffin reactions revealed no deficiency in the number or content of dense bodies (Table 3). The apparent increase in vacuolization in the patient's platelets (Fig 1) compared with the control platelets shown in Fig 2 is within the range of ultrastructural changes seen in control platelets prepared in the same manner. This dilation of the open canalicular system and the increase in microvilli (Fig 1) are commonly seen in activated platelets (ie, those exposed to glass). In contrast to the Wintrobe tube preparations, used for routine electron microscopy, the patient's platelets that were prepared for quantitative ultrastructural cytochemistry, with the use of only plastic tubing and plastic tubes, do not show this degree of vacuolization (Fig 3).

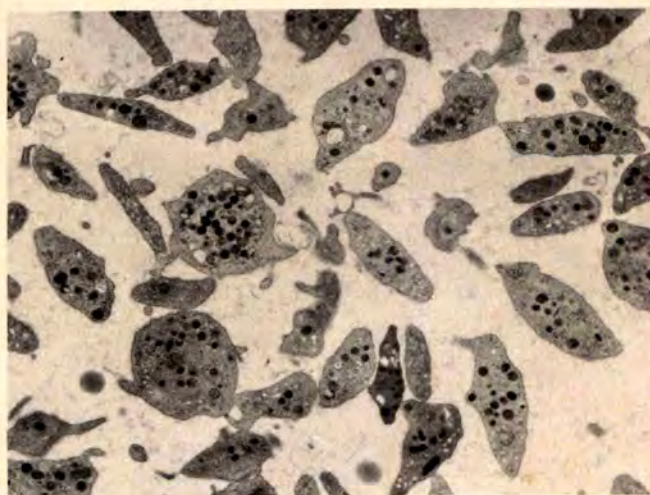


Fig 2.—Low-power electron micrograph of platelet profiles obtained from an age-matched control subject with no evidence of a bleeding disorder. Platelets contain a normal complement of organelles. Some of the platelets have a discoid shape and others exhibit pseudopodal extensions, the latter of which is indicative of platelet activation (uranyl acetate-lead citrate, original magnification $\times 8700$).

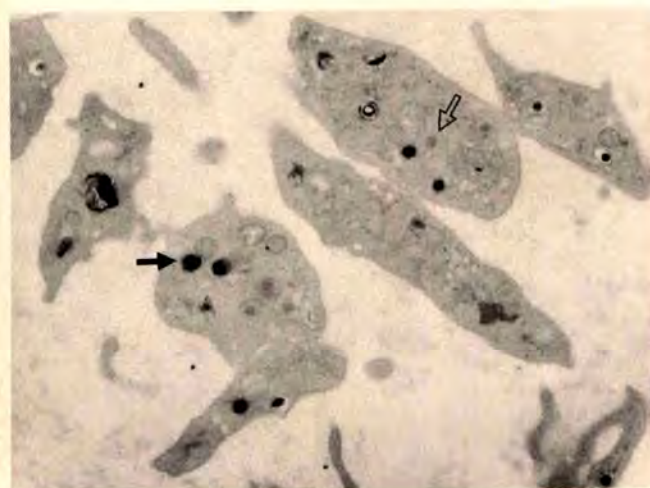


Fig 3.—Higher-power electron micrograph of platelet profiles obtained from the patient and fixed in a calcium-containing fixative for better visualization of the abundant platelet dense bodies (solid arrow). Alpha granules with their eccentric cores (open arrow) are readily identified (Weiss' fixative, postosmicated, no counterstain; original magnification $\times 18100$).

COMMENT

The initial laboratory test results in our patient of normal platelet count, prothrombin time, and partial thromboplastin time and prolonged bleeding time suggested that he had a disorder of platelet function. Further *ex vivo* platelet studies revealed abnormalities consistent with Glanzmann's thrombasthenia.

Glanzmann's thrombasthenia is a bleeding disorder characterized by platelets that fail to aggregate following stimulation with many agonists (eg, ADP, collagen, thrombin, and hexadimethrine bromide).^{5,21} The platelets generally have a low amount of glycoprotein IIb-IIIa, although a few patients with near-normal amounts of the

complex have been described.^{2,22,23} The glycoprotein IIb-IIIa complex is made available on activated platelets, and this complex can bind different adhesive proteins, such as fibrinogen, von Willebrand factor, fibronectin, and vitronectin.^{3,24,25} Fibrinogen binding appears to be a prerequisite for normal platelet aggregation.²⁴⁻²⁶ Platelet membrane glycoprotein Ib is the major receptor for von Willebrand factor.^{3,4} This receptor is present and functions normally in platelets from patients with thrombasthenia. Thus, activated thrombasthenic platelets will not aggregate (cell-to-cell interaction) because of either a deficiency or an abnormality of the glycoprotein IIb-IIIa complex. However, if the agonist is strong enough (eg, thrombin or a high concentration of ADP), the platelets will undergo a release/secretion reaction, but they will not aggregate.⁵

In the patient described herein, the platelets would not aggregate normally with the addition of a variety of agonists, including ADP and collagen. However, ATP release could be induced with thrombin and arachidonic acid. Electron microscopic studies of his platelets revealed normal morphologic features, dense body numbers and content of nucleotides, amines, and calcium. These findings eliminate storage pool disease as a cause of the platelet defect.

The patient's impaired response to ristocetin was unexpected. The inability of platelets to agglutinate with the addition of ristocetin is seen in von Willebrand's disease, which is due to reduced or an abnormal von Willebrand factor; the Bernard-Soulier syndrome, which is due to a deficiency of platelet glycoprotein Ib; and in storage pool/release defect diseases.^{3,4,27} Our patient had normal plasma levels of von Willebrand factor protein, von Willebrand factor activity (ristocetin cofactor assay), the presence of glycoprotein Ib on his platelets, normal numbers of dense bodies in his platelets, and the ability to release ATP with thrombin. Thus, his platelet aggregation after exposure to the antibiotic ristocetin should be the same as that of normal platelets.

Although platelet aggregation is primarily mediated by fibrinogen interactions with glycoprotein IIb-IIIa, von Willebrand factor can also function as a ligand to allow platelet aggregation.²⁵ The suboptimal response of our patient's and his sister's platelets to ristocetin (which is mediated through von Willebrand factor) may be a manifestation of an abnormal glycoprotein IIb-IIIa complex.

The only platelet agonist that caused platelet clumping was *Crotalus* snake venom. Rattlesnake venom causes a generalized membrane injury and probably does not act through a specific receptor site.¹⁹

The authors kindly acknowledge Douglas W. Cromey, MS, and Charles G. Bjore, Jr, MBA, for their excellent technical assistance.

The snake venom used in this study was a gift of Finley Russell, PhD, University of Arizona, Tucson.

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In Other AMA Journals

ARCHIVES OF SURGERY

The Value of Surgical History

Ira M. Rutkow, MD, MPH, DrPH
(*Arch Surg*. 1991;126:953-956)

Lichen Sclerosus et Atrophicus in Children

Vera Loening-Baucke, MD

● The symptoms, findings, associated conditions, and treatment of lichen sclerosus et atrophicus were studied in 10 girls and one boy. Lichen sclerosus et atrophicus is a benign but chronic condition of the anogenital area of girls and, less frequently, of boys. The characteristic lesions are hypopigmented plaques in a figure-of-8 pattern surrounding the vulva and anus and often involving the natal cleft. The affected hypopigmented skin is sharply demarcated from the normal skin. Hemorrhagic, bullous lesions are uncommon. Fissures and ulcers are seen on the labia, between the labia, and on the perineum, anus, and natal cleft in many children and on the glans penis in boys. Lichen sclerosus et atrophicus causes painful defecation and anal and vulval bleeding. In two patients, one girl and one boy, anal stenosis due to lichen sclerosus et atrophicus and laxative treatment developed. Lichen sclerosus et atrophicus mimics sexual abuse and has led to false accusation and investigations. The anogenital lesions cleared in three patients at the ages of 9, 11, and 12 years, but lesions can persist into adulthood. (*AJDC*. 1991;145:1058-1061)

Lichen sclerosus et atrophicus (LSA) is a benign but chronic condition of the epithelium and dermis and is characterized by ivory or white, shiny macules and papules that coalesce to form homogeneous hypopigmented plaques. The condition affects the vulvar and perianal areas of prepubertal girls and premenopausal women. It is most frequently seen in postmenopausal women. Boys as well as men can be affected. The major symptom in males is phimosis. The condition in females outnumbers that in males 10:1.¹

Lichen sclerosus et atrophicus is more common than is currently recognized, with 10% to 15% of all cases occurring in children. Anogenital LSA can mimic sexual abuse and has led to false accusations and investigations for sexual abuse.²⁻⁶ The mode of onset, clinical features, associated conditions, and treatment of this disease have received little attention in the pediatric literature. I report the symptoms, findings, associated conditions, and treatment in 10 girls and one boy to familiarize physicians with the range of appearances and the treatment of childhood LSA.

PATIENTS AND METHODS

Ten girls and one boy, 3 to 11 years of age, with skin changes of the anogenital region consistent with LSA were examined during a period of 3 years. These children had come to the General Pediatric Clinic or to the Encopresis Clinic at the University of Iowa, Iowa City, for evaluation of fecal soiling, constipation, severe pain with defecation, vulvar itching, vulvar bleeding, and dysuria. All patients had been studied previously, some on multiple occasions, but none had been diagnosed as having LSA before I examined them. All patients were reexamined at least once to make sure the skin lesions had responded to therapy, and their parents were interviewed by telephone at the time of this report, 3 months to 3.3 years later (mean, 1.8 years), to elicit information concerning the course of LSA, results of treatment, and the general health of the patients.

RESULTS

Clinical Features

The demographics and physical findings of these children, all of whom were white, are listed in the Table. Nine of the 11 patients had been symptomatic for more than 1 year. In two patients (patients 1 and 8), the symptoms had been present for only 3 and 4 months. The onset of LSA could not be assessed with certainty because many parents were not aware of the presence of skin lesions. One case (patient 1) had been reported for sexual abuse. In addition, the families of three girls (patients 2, 4, and 7) were intensively questioned about sexual abuse by multiple examiners. Problems with defecation, including painful bowel movements, constipation, fecal soiling, anal fissures, and anal stenosis, were the chief complaints in nine of 11 patients. Another patient had had severe difficulties with anal fissures 2 years before but not at the time of the diagnosis of LSA. One girl (patient 5) and one boy (patient 11) had been taking daily laxatives for years; they reported pencil-like stools and had developed anal stenosis. Both gave a history of large-caliber stools and painful bowel movements before the start of laxative treatment. The boy had fecal soiling frequently during the day and was also incontinent of stool at night.

Two patients complained of vulvar bleeding, three of perineal itching, and two of painful urination. The two youngest patients had severe itching of the perineum. Patient 7 complained of dysuria and spots of blood on her underwear for the last 8 months. She had two erythematous, excoriated, and desquamated fissures, 1.5 and 2 cm in length, between her labia minora and majora. These lesions had partially healed on several

Accepted for publication February 4, 1991.

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Presentation of Lichen Sclerosus et Atrophicus in 11 Children

Patient/ Sex/ Age, y	Symptoms							Involvement on Physical Examination					
	Vulvar Bleeding	Perineal Itching	Dysuria	Painful Defecation	Bloody Stools	Constipation	Encopresis	Figure- of-8*	Labial Sores	Perineum	Anal Canal	Natal Cleft	Anal Fissure
1/F/3.3	++‡	+	-	++	++	+/-	-	+	+	+	+	-	+
2/F/4.1	-	++‡	-	-	-	-	-	+/-	+	-	-	-	-
3/F/4.4	-	-	‡	+++	-	++	‡	+	-	+	+	+	-
4/F/4.7	-	-	-	+++	+	-	-	+	-	+	+	-	+
5/F/5.8	-	-	-	+++	+	-§	-	+	-	+	+Tight	-	-
6/F/7.7	-	-	-	+++‡	+	+++‡	+++‡	+	-	+	+	+	+
7/F/8.2	‡	+	‡	++	++	++	-	+	+	+	+	-	++
8/F/8.4	-	-	-	++	-	++	‡	+	-	+	+	+	+
9/F/10.2	-	-	-	+++	-	‡	++	+	-	+	+	-	-
10/F/11.8	-	-	-	+	+	++	+++‡	+	-	+	+	-	-
11/M/6.7	-	-	-	++§	-	-§	+++	+/-	Penile sores	...	+Tight	+	-

*Figure-of-8 appearance of a hypopigmented and sclerotic area seen anterior to the clitoris, involving the clitoris, the labia, and the perineum and encircling the anal canal.

‡Initial symptom.

‡Reason for visit.

§Receiving laxative treatment.

occasions but recurred. She had been examined by several specialists and treated with a multitude of creams containing estrogen, antibiotics, and polymyxin B sulfate-bacitracin zinc-neomycin sulfate-hydrocortisone; antibacterial detergents; and a course of oral cephalosporin before being diagnosed as having LSA. No patient gave a family history of LSA.

Physical Examination

In 10 of the 11 patients, the results of physical examination were entirely normal except for the skin changes in the anogenital area. Details on symptoms and anogenital skin changes are presented in the Table. All female patients showed the classic feature of hypopigmented plaques producing an hourglass or figure-of-8 pattern encircling the vulva and anus (Figure). Hemorrhagic, bullous lesions were seen in patient 1. Fissures and ulcers were seen on the labia, between the labia, on the perineum, and in the anal canal and natal cleft in many children and on the glans penis in the boy. In 10 children, the anus showed the same sclerotic plaques along the anal rugae, often reaching into the anal canal. Four children had anal fissures. In two patients (patients 5 and 11), the anal sphincter was very tight, and anal examination was possible only after dilation. One patient (patient 11) had extragenital LSA involving his fingers. His initial anogenital examination revealed a penis that was circumcised and free of lesions. The anus appeared hypopigmented, was surrounded by excoriations, and had prominent rugae. He had anal stenosis. The hypopigmented sclerotic lesions around the anus and in the natal cleft persisted, fissuring at times, and at times extended along the raphe toward the scrotum. He later developed sores on the glans penis. All lesions responded to 1% hydrocortisone ointment.

Treatment

All of the patients were treated with 1% hydrocortisone ointment twice daily until fissures and erosions had

healed. Subsequently, patients applied the ointment to their anogenital area only when symptoms recurred. The treatment was not curative, but it improved the skin condition. In the two patients with anal stenosis (patients 5 and 11), treatment with milk of magnesia was continued for 1 month and then stopped after the anogenital skin lesions had improved. The stools were normal in diameter, consistency, and frequency at follow-up 1.5 and 2.5 years later, respectively.

Course

These 11 children were followed up for 3 months to 3.3 years (mean, 1.8 years). In three, the anogenital lesions cleared completely (in patient 9 at age 12.2 years, in patient 10 at age 11.3 years, and in patient 11 at 8.8 years, respectively). The fissures healed in all patients, but the hypopigmented areas in the figure-of-8 configuration were still visible in seven, and 1% hydrocortisone ointment was used intermittently for anogenital irritation. In patient 2, the symptoms persisted 3 months later. None of the girls had had menarche on follow-up. Lichen sclerosus et atrophicus involving the fingers only persisted in patient 11.

COMMENT

Lichen sclerosus et atrophicus in childhood is more common than is currently recognized. It can occur at any age and in any race.^{2,7} It is most common in the anogenital region, but extragenital involvement has been reported, with involvement of the upper part of the trunk, forearm, neck, and face.⁸ The initial lesions of anogenital LSA are irregular ivory macules or papules that coalesce to form homogeneous, hypopigmented plaques producing a figure-of-8 pattern encircling the vulva and anus. The affected skin is sharply demarcated from the normal skin. The hymen is not involved. The skin becomes thin and fissured, is frag-



Anogenital area of patient 4. The typical hypopigmented, sclerotic figure-of-8 appearance encircling the genital and anal area is shown. The affected skin is sharply demarcated from the normal skin. A superficial perineal fissure from the posterior commissure to the anus occurred during the physical examination.

ile, and is easily traumatized by minimal pressure, resulting in bruising or bleeding. Trauma is often caused by the inexperienced examiner trying to pull the labia and buttocks apart for inspection. In particular, fissures in the midline of the perineum are easily produced. Purpura, telangiectasia, erosions, excoriations, blistering (usually hemorrhagic), and bleeding can be seen. The appearance of thinned skin with erosions and purpura may be mistaken for trauma, in particular for sexual abuse. Lichen sclerosus et atrophicus mimicking sexual abuse and leading to false accusations has been reported previously.²⁻⁶ The presence of LSA does not exclude sexual abuse, because LSA does occur at sites of trauma, and the trauma may be caused by sexual abuse.^{9,10}

The typical symptoms of anogenital LSA are itching, bleeding, and hemorrhagic blisters. Defecation problems have not been observed with the same frequency by other investigators. This could be due to several reasons: (1) my particular interest in childhood constipation and encopresis (six of the 11 patients had been referred to the Encopresis Clinic at the University of Iowa), (2) the possibil-

ity that the skin lesions in children with fecal soiling were overlooked because of feces covering the macerated area, and (3) attribution of the skin changes to chronic irritation by feces. Anal fissures, even with enormous large-diameter stools, are rarely seen in children older than 4 years and should raise suspicion of an underlying skin condition. A history of severe anal pain with defecation or anal bleeding should lead to a thorough anorectal examination.

Anogenital LSA is most often diagnosed clinically, but histologic examination of the involved skin can confirm the diagnosis in uncertain cases. Light microscopy shows hyperkeratosis with follicular plugging, atrophy of the malpighian layer, hydropic degeneration of the basal layer, edema and homogenization of collagen in the upper dermis, and an inflammatory infiltrate in the middermis.¹¹ The differential diagnosis of LSA includes vitiligo, morphea, perianal dermatitis, and postinflammatory hypopigmentation, eg, due to atrophic vulvitis or diaper dermatitis.

The cause of LSA is unknown and is most likely multifactorial. Enzyme deficiencies (elastase-type protease, 5- α -reductase), infection, and an immunologically mediated response to a variety of infectious processes, trauma, or friction have been discussed.¹¹

Lichen sclerosus et atrophicus in prepubertal boys is very uncommon.³ It has been suggested that LSA is the most common cause of phimosis in boys.^{12,13} In the uncircumcised patient, a thickened, constricting band forms 1 to 2 cm from the distal edge of the prepuce, commonly resulting in phimosis and adhesions. Lichen sclerosus et atrophicus of the glans penis has been less frequently observed in circumcised males.³ The involvement of the glans can lead to stenosis of the urethral meatus and urinary obstruction.¹⁴ Carcinoma can arise in preexisting LSA.^{3,15}

There is no established specific treatment for LSA. Topical corticosteroids are often of benefit, particularly for pruritus, soreness, and pain. They generally relieve symptoms and may retard the course of the disease. We used 1% hydrocortisone ointment twice daily, with improvement in all children. Fluorinated steroids have been suggested for those whose itching cannot be controlled with unfluorinated steroids.¹¹ The use of topical estrogen, progesterone, and androgens is not indicated in young children because of possible systemic effects.⁵ Others have suggested that especially progesterone in oil or estrogen can be used safely and sometimes effectively in prepubertal girls.¹⁶

It is anticipated that approximately two thirds of premenarchal girls will have improvement or clearing of their lesions before or about the time of menarche.¹⁷ Long-term prospective studies are still lacking in childhood LSA. Children with persistence of the anogenital LSA will have to be followed up because complications due to atrophy of the labia minora and clitoris and constriction of the vaginal introitus or urethral meatus can occur. The cancer risk in LSA lesions in childhood is probably insignificant, but it is suggested to be 5% in adult women.

I have not seen previous reports of anal stenosis due to LSA. Two of my patients had developed anal stenosis. I think that the laxative treatment allowed the anal stenosis to develop and that daily anal dilation by a normalized stool would have prevented the development of

stenosis in anal LSA. In addition, the observation of anal involvement in male patients has not been previously reported.

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In Other AMA Journals

ARCHIVES OF NEUROLOGY

Spinal Tumors in Children and Adolescents: The International Review of Child Neurology

Ignacio Pascual-Castroviejo, Reviewed by Henry S. Schutta, MD
(*Arch Neurol*. 1991;48:786)

Diagnostic Criteria for Multiple Sclerosis Research Involving Multiply Affected Families

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(*Arch Neurol*. 1991;48:805-807)

Treatment of Ulcerated Hemangiomas With the Pulsed Tunable Dye Laser

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• Hemangiomas are the most common tumor of infancy and are characterized by rapid growth during the first 6 months of life. During the rapid growth phase, approximately 5% to 10% of the hemangiomas ulcerate. Ulcerated lesions are painful, may bleed, and are at risk for bacterial infection. Previous therapy has included daily local wound care, topical antibiotics, and local and systemic steroids. We treated nine infants (eight female and one male) with ulcerated hemangiomas by means of a vascular-specific (585-nm) pulsed (450-microsecond) tunable dye laser. Eight of the nine patients had a single ulceration, whereas one patient had two ulcerations within a large hemangioma. Six of the ulcerations healed with a single laser treatment. One ulceration required two treatments to heal, and the remaining two required three treatments. Pain was subjectively decreased within 2 to 3 days in all patients after a single treatment. The pulsed tunable dye laser should be considered in the treatment of all ulcerated hemangiomas.

(*AJDC*. 1991;145:1062-1064)

Hemangiomas are common tumors of infancy. They have a well-defined course consisting of an early rapid growth phase, followed by slow involution in most cases.¹⁻³ Since most hemangiomas regress, many authorities recommend treatment only for those hemangiomas that cause medical complications, such as obstruction (vision, breathing, defecation, or urination), high-output cardiac failure, and consumption coagulopathy. The treatment of choice in these situations is high-dose systemic glucocorticosteroids.⁴

Most hemangiomas do not fit into any of the above categories, do not require treatment with systemic steroids, and do not produce systemic complications. However, they are not without local complications. These include ulceration and infection during the rapid growth phase, and redundant skin folds, pigmentary changes, and fibrofatty deposits remaining after involution.⁵ Ulceration of the hemangiomas occurs in 5% to 10% of cases.⁵ This

may cause severe discomfort for the child, scarring of the affected area, and an increased likelihood of infection and hemorrhage. Treatment of ulcerated hemangiomas is often difficult and has consisted of topical antibiotics, occlusive or semioclusive barriers, and locally injected glucocorticosteroids, as well as systemic steroids.⁵

Pulsed tunable dye lasers were developed for the treatment of port-wine stains.^{6,7} They are also approved by the Food and Drug Administration for the treatment of hemangiomas and have been reported to be effective in selected cases.^{8,9} Because of the pain with ulcerated hemangiomas and the lack of fully effective therapy, we treated ulcerated hemangiomas with the pulsed tunable dye laser.

PATIENTS AND METHODS

Nine patients with ulcerated hemangiomas presented to either the Birthmark Treatment Center at the University of Colorado School of Medicine, Denver, or the Laser Center at Boston (Mass) City Hospital. The results are summarized in the Table. All of the hemangiomas ulcerated and became painful during the rapid growth phase, and the patients were brought in for treatment between 2 and 6½ months of age. Eight of the nine lesions were in the diaper area. Most of the patients had a single ulceration, while one female infant had two distinct ulcerations within a large hemangioma. The ulcerations were 3 to 35 mm in diameter and had been present for between 3 and 12 weeks before treatment.

All patients were treated with a vascular-specific (585-nm) pulsed (450-microsecond) dye laser (Candela SPTL-1, Candela Corp, Wayland, Mass). The entire hemangioma, not just the ulcerated portion, was treated during each visit. All of the ulcer bases were clean at the time of treatment.

All treatments were performed with a laser energy of 6.0 to 6.5 J/cm². Patients were treated every 2 to 4 weeks without anesthesia. Posttreatment care consisted of frequent application of bacitracin ointment. None of the patients received any previous or concomitant treatment.

RESULTS

Six of the 10 ulcers healed within 2 weeks with a single treatment, two healed after two treatments, and the other two required three treatments. In each of our patients, before the initial laser treatment, the parents reported the child to be in pain. Pain was subjectively eliminated in all patients after a single treatment. Parents reported that as early as the day after treatment the child's pain had subsided. Pain relief lasted as long as the patients were followed up. No injections after the treatments were re-

Accepted for publication April 4, 1991.

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Patients With Ulcerated Hemangiomas

Patient/Sex	Location	Age at 1st Treatment, mo	No. and Size (mm) of Ulcerations	Time Ulcerated Before Treatment, wk	No. of Treatments to Healing
1/F	L buttock	5	2, 35, and 15	6 and 4	2 and 1
2/F	Vulva	3.5	1, 9	8	1
3/M	Neck	6.5	1, 25	3	3
4/F	Perianal	5	1, 21	12	1
5/F	Perineal	4.5	1, 3	3	1
6/F	Vulva	6.5	1, 20	4	2
7/F	R buttock	3	1, 5	3	1
8/F	Vulva	4	1, 25	4	3
9/F	Perineal	2	1, 5	6	1

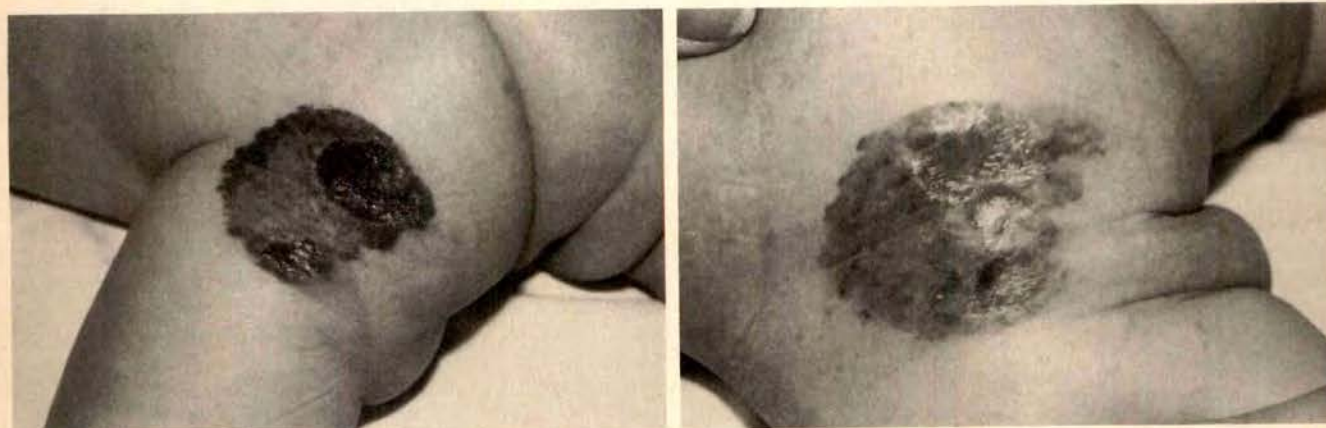


Fig 1.—Left, Ulcerated hemangioma of the buttock in a 5-month-old white girl. Right, Same hemangioma 1 month later after two laser treatments.

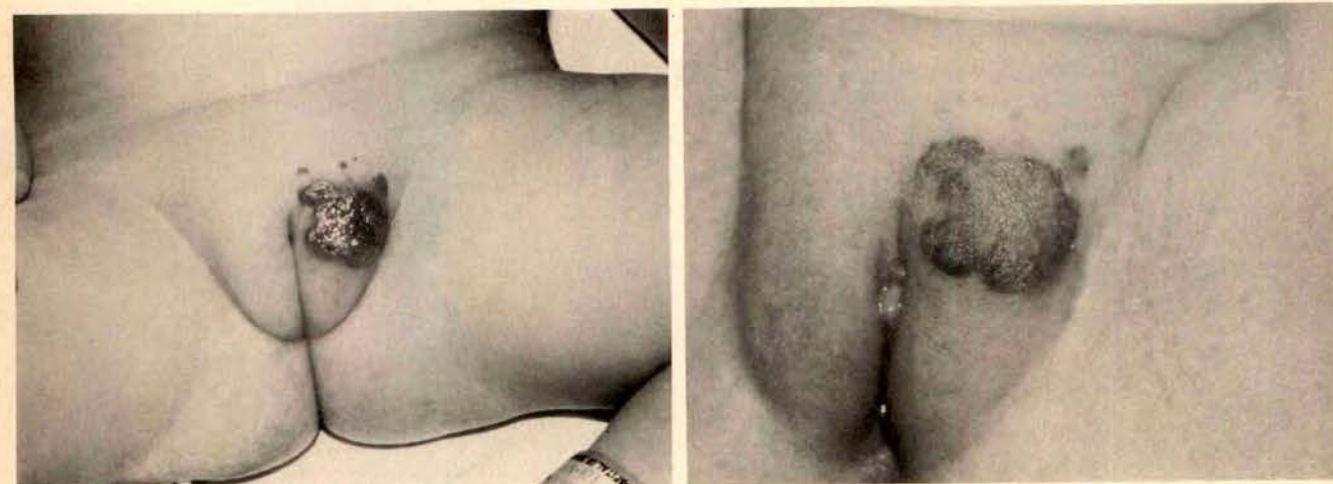


Fig 2.—Left, Ulcerated hemangioma of the vulva in a 6½-month-old white girl. Right, Same hemangioma 1 month later after two laser treatments.

ported. Figures 1 and 2 show patients 1 and 6, respectively, before and after treatment.

COMMENT

Ulceration of these lesions is a relatively common problem for which only supportive therapy has been available. Treatment of ulcerated hemangiomas with a vascular-specific pulsed dye laser leads to rapid healing of

the ulcerated area. This therapy also decreases the associated pain, minimizes the risk of infection, and decreases the eventual scarring by preventing enlargement of the ulceration.

The mechanism of hemangioma ulceration is poorly understood. These lesions almost always ulcerate during their rapid growth phase. Ulceration also tends to occur in mixed superficial and deep hemangiomas located in

areas of trauma and frequent movement. Eight of the nine ulcerated hemangiomas that we treated were located in the diaper area.

The mechanism of wound healing in ulcerated hemangiomas is also poorly understood. Vascular-specific pulsed dye lasers function by selective photothermolysis of capillary-sized blood vessels. It is possible that thermal damage to the vessels at the surface of the ulcerated hemangioma leads to the release of factors that stimulate wound healing, although this is speculative.

All of the ulcerations that were less than 20 mm healed completely within 2 weeks after a single treatment. The very large (>20 mm) ulcerations required two to three treatments, but all had begun healing after one treatment. It is possible that, given more time, they would have resolved with a single treatment. No side effects were noted.

This form of tumor destruction appears to accelerate the natural processes leading to tumor regression. After treatment, the hemangiomas often began to develop central pallor.

We suggest that vascular-specific pulsed dye lasers are safe and effective for the treatment of mixed superficial and deep hemangiomas that have ulcerated during the rapid growth phase. It is optimal to treat the hemangiomas as soon as an ulceration is noted, because ulcerations of less than 20 mm may heal within 2 weeks, and the pain associated with the ulcerated hemangioma diminishes within 24 hours after a single treatment. We believe that

pulsed dye laser therapy should be considered as a treatment option for ulcerated hemangiomas.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Drug Abuse Treatment as a Strategy to Prevent Human Immunodeficiency Virus Infection Among Intravenous Drug Users: How Can We Maximize Prevention of Infection?

A. Preston West
(*Arch Intern Med*. 1991;151:1493-1496)

Legal Myths About Terminating Life Support

Alan Meisel, JD
(*Arch Intern Med*. 1991;151:1497-1502)

New Medicare

Arthur Vall-Spinosa, MD
(*Arch Intern Med*. 1991;151:1503-1509)

The Adverse Effects of Hospitalization on Drug Regimens

Deborah M. Omori, MD; Roger P. Potyk, PharmD; Kurt Roenke, MD
(*Arch Intern Med*. 1991;151:1562-1564)

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See adjacent page for Brief Summary of prescribing information.

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Brief Summary

DESCRIPTION: PEDIAPRED Oral Liquid is a dye free, colorless to light straw colored, raspberry flavored solution. Each 5 ml (teaspoonful) of PEDIAPRED contains 6.70 mg prednisolone sodium phosphate (5.00 mg prednisolone base) in a palatable, aqueous vehicle.

INDICATIONS AND USAGE: PEDIAPRED Oral Liquid is indicated in the following conditions:

1. **Endocrine Disorders**—Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; hypercalcemia associated with cancer; nonsuppurative thyroiditis
2. **Rheumatic Disorders**—As adjunctive therapy for short term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; post-traumatic osteoarthritis; synovitis of osteoarthritis; epicondylitis
3. **Collagen Diseases**—During an exacerbation or as maintenance therapy in selected cases of: systemic lupus erythematosus; systemic dermatomyositis (polymyositis); acute rheumatic carditis
4. **Dermatologic Diseases**—Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative dermatitis; mycosis fungoides; severe psoriasis; severe seborrheic dermatitis
5. **Allergic States**—Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in: seasonal or perennial allergic rhinitis; bronchial asthma; contact dermatitis; atopic dermatitis; serum sickness; drug hypersensitivity reactions
6. **Ophthalmic Disorders**—Severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as: allergic conjunctivitis; keratitis; allergic corneal marginal ulcers; herpes zoster ophthalmicus; iritis and iridocyclitis; choroiditis; anterior segment inflammation; diffuse posterior uveitis and choroiditis; optic neuritis; sympathetic ophthalmia
7. **Respiratory Disorders**—Symptomatic sarcoidosis; Loeffler's syndrome not manageable by other means; berylliosis; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; aspiration pneumonia
8. **Hematologic Disorders**—Idiopathic thrombocytopenic purpura in adults; secondary thrombocytopenia in adults; acquired (autoimmune) hemolytic anemia; Erythroblastopenia (RBC anemia); congenital (erythroid) hypoplastic anemia
9. **Neoplastic Disorders**—For palliative management of: leukemias and lymphomas in adults; acute leukemia of childhood
10. **Edematous States**—To induce a diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
11. **Gastrointestinal Disorders**—To tide the patient over a critical period of the disease in: ulcerative colitis; regional enteritis
12. **Nervous System**—Acute exacerbations of multiple sclerosis
13. **Miscellaneous**—Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy; trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS: Systemic fungal infections.

WARNINGS: In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.

Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. **While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high doses, because of possible hazards of neurological complications and a lack of antibody response.**

The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

PRECAUTIONS: General: Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation. The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See DOSAGE AND ADMINISTRATION.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Information for Patients: Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision, to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection.

Drug Interactions: Drugs such as barbiturates which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of PEDIAPRED be increased.

Pregnancy: Pregnancy Category C: Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Animal studies in which prednisolone has been given to pregnant mice, rats and rabbits have yielded an increased incidence of cleft palate in the offspring.

Nursing Mothers: Prednisolone is excreted in breast milk, but only to a small (less than 1% of the administered dose) and probably clinically insignificant extent. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

ADVERSE REACTIONS:

Fluid and Electrolyte Disturbances

Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension

Musculoskeletal

Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones

Gastrointestinal

Peptic ulcer with possible perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis

Dermatologic

Impaired wound healing; thin fragile skin; petechiae and ecchymoses; facial erythema; increased sweating; may suppress reactions to skin tests

Metabolic

Negative nitrogen balance due to protein catabolism

Neurologic

Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache

Endocrine

Menstrual irregularities; development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetes

Ophthalmic

Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos

OVERDOSAGE: The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children. Treatment of acute overdosage is by immediate gastric lavage or emesis. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

CAUTION: Federal law prohibits dispensing without prescription.

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[Meningococcal Protein Conjugate] | MSD)

The only Haemophilus b vaccine with a 2-dose primary regimen

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A booster dose should be administered in infants completing the primary 2-dose regimen before 12 months of age.

PedvaxHIB is contraindicated in patients who are hypersensitive to any component of the vaccine or the diluent.

For a Brief Summary of Prescribing Information, please see next page.

For most infants,
Predictable

PedvaxHIB®

(Haemophilus b Conjugate Vaccine
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INDICATIONS AND USAGE: PedvaxHIB is indicated for routine immunization against invasive disease caused by *Haemophilus influenzae* type b in infants and children 2 to 71 months of age.

PedvaxHIB will not protect against disease caused by *Haemophilus influenzae* other than type b or against other microorganisms that cause invasive disease, such as meningitis or sepsis.

Revaccination: Infants completing the primary two-dose regimen before 12 months of age should receive a booster dose (see DOSAGE AND ADMINISTRATION).

Use with Other Vaccines: Studies have been conducted in which PedvaxHIB has been administered concomitantly with the primary vaccination series of DTP and OPV, or concomitantly with M-M-R® II (Measles, Mumps, and Rubella Virus Vaccine Live, MSD) (using separate sites and syringes), or with a booster dose of OPV plus DTP (using separate sites and syringes for PedvaxHIB and DTP). No impairment of immune response to individual tested vaccine antigens was demonstrated. The type, frequency, and severity of adverse experiences observed in these studies with PedvaxHIB were similar to those seen when the other vaccines were given alone.

PedvaxHIB IS NOT RECOMMENDED FOR USE IN INFANTS YOUNGER THAN 2 MONTHS OF AGE.

CONTRAINDICATIONS: Hypersensitivity to any component of the vaccine or the diluent.

WARNINGS: USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED. If PedvaxHIB is used in persons with malignancies or in those who are receiving immunosuppressive therapy or who are otherwise immunocompromised, the expected immune response may not be obtained.

PRECAUTIONS: General: As for any vaccine, adequate treatment provisions, including epinephrine, should be available for immediate use should an anaphylactoid reaction occur. As with other vaccines, PedvaxHIB may not induce protective antibody levels immediately following vaccination. As with any vaccine, vaccination with PedvaxHIB may not result in a protective antibody response in all individuals given the vaccine. As reported with Haemophilus b polysaccharide vaccine and another Haemophilus b conjugate vaccine, cases of Haemophilus b disease may occur in the week after vaccination, prior to the onset of the protective effects of the vaccines. There is insufficient evidence that PedvaxHIB given immediately after exposure to natural *Haemophilus influenzae* type b will prevent illness. Any acute infection or febrile illness is reason for delaying use of PedvaxHIB except when, in the opinion of the physician, withholding the vaccine entails a greater risk.

Laboratory Test Interactions: Sensitive tests (e.g., Latex Agglutination Kits) may detect PRP derived from the vaccine in urine of some vaccinees for up to seven days following vaccination with PedvaxHIB; in clinical studies with PedvaxHIB, such children demonstrated normal immune response to the vaccine.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: PedvaxHIB has not been evaluated for its carcinogenic or mutagenic potential or for its potential to impair fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with PedvaxHIB. It is also not known whether PedvaxHIB can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PedvaxHIB is not recommended for use in pregnant women.

ADVERSE REACTIONS: In early clinical studies involving the administration of 8,086 doses of PedvaxHIB alone to 5,027 healthy infants and children 2 months to 71 months of age, PedvaxHIB was generally well tolerated. No serious adverse reactions were reported. During a two-day period following vaccination with PedvaxHIB in a subset of these infants and children, the most frequently reported adverse reactions, excluding those shown in the first table, in decreasing order of frequency, included: irritability, sleepiness, respiratory infection/symptoms, and ear infection/otitis media. Urticaria was reported in two children. Thrombocytopenia was seen in one child. A cause-and-effect relationship between these side effects and the vaccination has not been established.

Selected objective observations reported by parents over a 48-hour period in infants and children 2 to 71 months of age following primary vaccination with PedvaxHIB alone are summarized in the first table.

In The Protective Efficacy Study, 4,459 healthy Navajo infants 6 to 12 weeks of age received PedvaxHIB or placebo. Most of these infants received DTP/OPV concomitantly. No differences were seen in the type and frequency of serious health problems expected in this Navajo population or in serious adverse experiences reported among those who received PedvaxHIB and those who received placebo, and none was reported to be related to PedvaxHIB. Only one serious reaction (tracheitis) was reported as possibly related to PedvaxHIB and only one (diarrhea) as possibly related to placebo. Seizures occurred infrequently in both groups (9 occurred in vaccine recipients, 8 of whom also received DTP; 8 occurred in placebo recipients, 7 of whom also received DTP) and were not reported to be related to PedvaxHIB. The frequencies of fever and local reactions occurring in a subset of these infants during a 48-hour period following each dose were similar to those seen in early clinical studies (see first table).

As with any vaccine, there is the possibility that broad use of PedvaxHIB could reveal adverse reactions not observed in clinical trials.

Potential Adverse Reactions: The use of Haemophilus b polysaccharide vaccines and another Haemophilus b conjugate vaccine has been associated with the following additional adverse effects: early onset of Haemophilus b disease and Guillain-Barré syndrome. A cause-and-effect relationship between these side effects and the vaccination was not established.

Fever or Local Reactions in Subjects 2 to 71 Months of Age Vaccinated with PedvaxHIB Alone: Other Clinical Studies

Age (Months)	Reaction	Number of Subjects Evaluated	Dose 1			Number of Subjects Evaluated	Dose 2		
			6 hr	24	48		6 hr	24	48
2-14*	Fever >38.3°C (101°F)	532	2.4%	3.8%	1.9%	329	3.0%	4.3%	3.6%
	Erythema >2.5 cm diameter	1,026	0.2%	1.0%	0.4%	585	0.9%	1.2%	0.7%
	Swelling/Induration >2.5 cm diameter	1,026	0.6%	1.5%	1.6%	585	0.9%	2.8%	3.7%
15-71**	Fever >38.3°C (101°F)	149	4.0%	4.0%	6.7%				
	Erythema >2.5 cm diameter	572	0.0%	0.3%	0.2%				
	Swelling/Induration >2.5 cm diameter	572	0.9%	2.1%	1.4%				

*Additional complaints reported following vaccination with the first and second dose of PedvaxHIB, respectively, in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (101, 41), crying for more than one-half hour (43, 15), rash (16, 17), and unusual high-pitched crying (4, 4).

**Additional complaints reported following vaccination with one dose of PedvaxHIB in the indicated number of subjects were: nausea, vomiting, and/or diarrhea (44), crying for more than one-half hour (19), rash (12), and unusual high-pitched crying (0).

DOSAGE AND ADMINISTRATION:

FOR INTRAMUSCULAR ADMINISTRATION. DO NOT INJECT INTRAVENOUSLY.

2 to 14 Months of Age: Infants 2 to 14 months of age should receive a 0.5-mL dose of vaccine ideally beginning at 2 months of age followed by a 0.5-mL dose 2 months later (or as soon as possible thereafter). When the primary two-dose regimen is completed before 12 months of age, a booster dose is required (see text and second table).

15 Months of Age and Older: Children 15 months of age and older previously unvaccinated against *Haemophilus b* disease should receive a single 0.5-mL dose of vaccine.

Booster Dose: In infants completing the primary two-dose regimen before 12 months of age, a booster dose (0.5 mL) should be administered at 12 months of age but not earlier than 2 months after the second dose.

DATA ARE NOT AVAILABLE REGARDING THE INTERCHANGEABILITY OF OTHER HAEMOPHILUS b CONJUGATE VACCINES AND PedvaxHIB® (Haemophilus b Conjugate Vaccine [Meningococcal Protein Conjugate], MSD).

Vaccination Regimens by Age Group (see text for details)

Age (Months) at First Dose	Primary	Age (Months) at Booster Dose
2-10	2 doses, 2 months apart	12
11-14	2 doses, 2 months apart	—
15-71	1 dose	—

TO RECONSTITUTE, USE ONLY THE ALUMINUM HYDROXIDE DILUENT SUPPLIED.

First, agitate the diluent vial; then, using sterile technique, withdraw the entire volume of aluminum hydroxide diluent into the syringe to be used for reconstitution. Inject all the aluminum hydroxide diluent in the syringe into the vial of lyophilized vaccine, and agitate to mix thoroughly.

Withdraw the entire contents into the syringe and inject the total volume of reconstituted vaccine (0.5 mL) intramuscularly, preferably into the anterolateral thigh or the outer aspect of the upper arm.

It is recommended that the vaccine be used as soon as possible after reconstitution. Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours. Agitate prior to injection.

Parenteral drug products should be inspected visually for extraneous particulate matter and discoloration prior to administration whenever solution and container permit. Aluminum hydroxide diluent and PedvaxHIB when reconstituted are slightly opaque white suspensions.

Special care should be taken to ensure that the injection does not enter a blood vessel.

It is important to use a separate sterile syringe and needle for each patient to prevent transmission of hepatitis B or other infectious agents from one person to another.

HOW SUPPLIED: No. 4792—PedvaxHIB is supplied as a single-dose vial of lyophilized vaccine, NDC 0006-4792-00, and a vial of aluminum hydroxide diluent.

No. 4797—PedvaxHIB is supplied as follows: a box of 5 single-dose vials of lyophilized vaccine, NDC 0006-4797-00, and 5 vials of aluminum hydroxide diluent.

Storage: Before reconstitution, store PedvaxHIB at 2° to 8°C (36° to 46°F). Store reconstituted vaccine in the vaccine vial at 2° to 8°C (36° to 46°F) and discard if not used within 24 hours.

DO NOT FREEZE the aluminum hydroxide diluent or the reconstituted vaccine.

For more detailed information, consult your MSD Representative or see Prescribing Information.

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ROCHESTER, NEW YORK - Opportunity for a general pediatrician to develop their practice as part of the Rochester Medical Group pediatric department. Rochester Medical Group is a multi-specialty group practice which cares for fee-for-service as well as prepaid patients. In addition to full-time position, willing to consider part-time or job-share opportunities. Subspecialty interests possible. University affiliation encouraged. Competitive salary and benefits. Located in attractive metropolitan area with many cultural and recreational advantages. Send resume or call: Rochester Medical Group, P.C. Attention: James Tobin, MD, 800 Carter Street, Rochester, NY 14621. (716) 338-1400. EOE, M/F.

LARGE MULTI-SPECIALTY GROUP in northern Virginia area needs bilingual (Spanish) pediatrician to replace retiring physician of forty years. Send CV to: Medical Director, Falls Church Medical Center, 6060 Arlington Boulevard, Falls Church, VA 22044.

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UPSTATE NEW YORK - BC/BE pediatrician wanted to join two pediatricians in semi-rural Columbia County. Part-time now. Full-time in one-three years. 2½ hours to New York City or Boston. ½ hour to skiing or Tanglewood. An opportunity for someone interested in practicing good pediatrics and enjoying living. Send CV to: Ira Marks, MD, Chatham, NY 12037.

MISSOURI - Moberly, a city of 13,000, 36 miles north of Columbia, Missouri, seeks a BE/BC pediatrician. Modern 120-bed hospital. Beautiful countryside, many lakes, AAA schools. Great benefits, guaranteed income. Call: Barb Shipley at (800) 638-6942.

COME TO MONTANA! Pediatrician, BC/BE needed to join expanding high volume, nine member multi-specialty group. Development of new subregional medical campus. Excellent opportunity plus attractive financial package. Located in east-central Montana along Yellowstone River. Great outdoors for recreation, hunting and fishing. Excellent educational system. Lifestyle is rural and family oriented. Send CV to: Administrator, Garberson Clinic, 2200 Box Elder, Miles City, MT 59301.

AUSTIN, TEXAS - Seeking general pediatrician BE/BC for full time position. Call or write: Mrudula Deshpande, MD, 13740 Research, V-1, Austin, TX 78750. (512) 250-0406.

NEW YORK - BC/BE pediatrician to join an established solo practice in Orange County. Sixty minutes northwest of New York City. Pleasant working conditions. Progressive community hospital. Send CV: Box #122, c/o AJDC.

Professional Opportunities

PHILADELPHIA – Children's Hospital of Philadelphia seeks BC/BE pediatricians for its general pediatric practices. Exciting opportunity to practice in an academic setting. Responsibilities include ambulatory patient care and clinical teaching (affiliated with UPenn Medical School). Opportunities for clinical research and in-patient supervision. Competitive salary and excellent fringe benefits. Send CV to: Frances M. Gill, MD, Suite 2013, General Pediatrics, 1 Children's Plaza, Philadelphia, PA 19104. Children's Hospital of Philadelphia is an equal opportunity/affirmative action employer.

SOUTHERN CALIFORNIA – Established pediatric practice available. Prestige location, \$250,000 gross and growing. Reply to: V. Hemingway, P.O. Box 11792, Costa Mesa, CA 92627.

ARIZONA – BC/BE pediatrician to join three-doctor partnership, guaranteed income, fringes, incentives. Growing community, pines, family recreation, arts. Send CV: James Mick, MD, 919 12th Place #3, Prescott, AZ 86301. (602) 778-4581.

ATTENTION PHYSICIAN RECRUITERS. The "Classified Advertising" sections now in all nine AMA Specialty Journals target the physician you want. These highly visible sections put your message in the hands of every specialist that qualifies for your professional opportunity, every month. To place the ad of your choice, any size, call toll free: (800) 237-9851; local (813) 443-7666.

PENNSYLVANIA – Pediatrician needed. \$130,000 net plus M/P insurance, full benefits, new office and operating expenses provided. One in four call. Built-in referrals. Population 200,000. Must be a dynamic self-starter interested in clinical practice development, recruiting pediatricians, development of pediatric services clinic. Must be board-certified. Call or send CV to: Perry Robinson, Cejka & Co., 222 South Central, Suite 700, St. Louis, MO 63105. (800) 765-3055.

HAWAII – PEDIATRICIAN: Opportunity with an established and growing multi-specialty group practice. Competitive compensation and excellent benefits. If working with congenial associates in a quality oriented environment is for you, why not consider relocating to the Hawaiian Islands? Send CV or call: Rex Couch, MD, Medical Director, Kauai Medical Group, Inc., 3420-B Kuhio Highway, Lihue, HI 96766. (808) 246-1624.

BC/BE PEDIATRICIAN needed July 1, 1991 for full-time hospital based position covering Level I-II Nursery and pediatric emergency patients. Suburban St. Louis community hospital in affiliation with tertiary-care pediatric center with academic opportunities available. Competitive salary, excellent benefits, time to pursue outside interests, and no off-site call. Send curriculum vitae to: Richard Barry, MD, St. Louis University Department of Pediatrics, Cardinal Glennon Children's Hospital, 1465 South Grand Boulevard, St. Louis, MO 63104. (314) 577-5360. M/F/H/V. EEO employer. Women and minorities encouraged to apply.

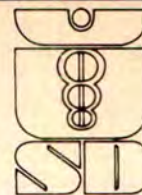
ENJOY PRACTICING PEDIATRICS in western North Carolina. BC/BE pediatrician needed to join busy, well established private practice in Murphy, North Carolina, the heart of the Great Smokies. Beautiful area with exceptional recreational opportunities such as backpacking, whitewater rafting, etc. Quiet, safe community. Affiliated with modern, progressive small hospital currently expanding. Excellent family-oriented life-style opportunity. Competitive salary with potential practice buy-in. Send CV to: Pamela Boland, MD, 2000 Highway 64E, Suite 135, Murphy, NC 28906. (704) 837-2128.

WEST COAST, CENTRAL FLORIDA – 154-bed not-for-profit medical facility. Set up pediatric department to your specifications. Guarantee. Contact: Leona Gans (813) 541-5336.

PLEASE NOTE – Address replies to box number ads as follows: Box number _____, c/o AJDC, P.O. Box 1510, Clearwater, FL 34617.

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The University of South Dakota School of Medicine currently has openings for BE/BC pediatric subspecialties.

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Carl Hinson • (800) 468-3333

USD School of Medicine
1100 South Euclid, P.O. Box 5039
Sioux Falls, SD 57117

PENNSYLVANIA – BC pediatrician in north central Pennsylvania seeks BC/BE associate to join challenging rural practice. Position offers excellent salary and benefits with potential for loan repayment. Affiliated hospital has 160 beds (55 long term care), Level I Nursery, and multi-specialist physician staff. Area features a wide variety of outdoor activities, including hiking, skiing, biking, fishing, and hunting. Reply to: Jan Freeman Kinsley, Physician Recruiter, at (814) 274-0229. Or send curriculum vitae to: Charles Cole Memorial Hospital, U.S. Route 6, Coudersport, PA 16915.

BC/BE PEDIATRICIAN to join two BC private practice pediatricians in upstate New York, Thousand Islands region. Affiliation leading to partnership. Level II NICU, cystic fibrosis center. Stimulating practice with an on-call arrangement with other pediatricians, excellent recreational facilities and schools in a thriving small city with many cultural advantages. A good place to raise children, too. Contact: R.G. Perciaccante, MD, 199 Pratt Street, Watertown, NY 13601.

ALABAMA/PEDIATRICIAN – BE/BC to join established practice. Modern office with experienced staff. 400-bed hospital with neonatologists and Level III NICU. Shared call arrangement, full call every 5th weekend. Community of 200,000, mild climate, lovely housing, excellent schools. Three hour drive to Florida beaches and Atlanta, Georgia. Send CV to: Robert Beshear, MD, 3401 Eastern Boulevard, Montgomery, AL 36116.

SECOND BC/BE NEONATOLOGIST for rural, university community, fifteen miles from beautiful Lake Michigan and 1½ hours from Chicago. Private practice, 24-bed, Level II+ NICU. Contact: Ann M. Himo, MD, Department of Neonatology, Porter Memorial Hospital, Valparaiso, IN 46383. (219) 465-4699.

PEDIATRICIAN: Five person group seeking full-time BE/BC pediatrician. Fully equipped office in Lexington, Kentucky. Nearby tertiary care residency program. Competitive salary and benefit package. Send CV: M.J. Harris, Pediatric & Adolescent Associates, 2620 Wilhite Drive, Lexington, KY 40503.

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Faculty Positions

WYOMING – University of Wyoming Family Practice Residency-Casper is seeking an experienced, clinically oriented, board-certified pediatrician to be the pediatric coordinator of an 8-8 family practice residency program. Level II Nursery skills are a must. 60% teaching, 20% direct patient care, 20% research. This is a tenure track position. University approval will be required prior to filling this position. Come join us in beautiful Wyoming! Contact: Dr. David Driggers, Director, University of Wyoming Family Practice Residency, 1522 East "A" Street, Casper, WY 82601. (307) 266-3076. The University of Wyoming is an affirmative action/EOE.

CALIFORNIA – General pediatrician. The Department of Pediatrics, UCLA School of Medicine, is seeking an academic general pediatrician at the assistant or associate professor level to participate in a program in ambulatory and inpatient pediatrics at the Los Angeles County, Olive View Medical Center. An interest in infectious disease or pulmonary disease is desirable. Olive View is an integral part of the UCLA teaching and research program sharing house staff, faculty and research facilities. The ability to obtain a California license is required. Applicants should send their curriculum vitae to: S. Douglas Frasier, MD, Chief of Pediatrics, Olive View Medical Center, 14445 Olive View Drive, Suite 3A108, Sylmar, CA 91342. Equal opportunity employer M/F.

ACADEMIC PEDIATRIC NEUROLOGIST – The Department of Pediatrics of The Ohio State University College of Medicine and Children's Hospital, Columbus, is seeking a fifth pediatric neurologist at the assistant to full professor level. Candidates must be board-certified or -eligible in neurology with special competence in child neurology. Subspecialty expertise in the management of epilepsy is desirable. Special consideration will be given to applicants with a strong background in the development and implementation of clinical research studies, especially studies involving experimental drug therapy of epilepsy. Duties will include teaching, patient care and research. This position offers challenging opportunities for academic growth and development in the neurosciences. The Children's Hospital in Columbus is the major pediatric facility for south central Ohio and is the pediatric teaching hospital for the Ohio State University College of Medicine. The Division of Pediatric Neurology has a diverse clinical program which includes a well-equipped clinical neurophysiology laboratory. Ongoing NIH-funded research in the division includes acute treatment of seizures and the neurophysiology of bacterial brain infection. For further information contact: Francis S. Wright, MD, Division of Neurology, Department of Pediatrics, Children's Hospital, 700 Children's Drive, Columbus, OH 43205. Telephone: (614) 461-6742. The Ohio State University is an equal opportunity/affirmative action employer.

GENERAL PEDIATRICS: Director of Ambulatory Services – The University of California, Davis, Department of Pediatrics, is seeking an academic physician who is board-certified with proven excellence in clinical care, teaching, research and administrative abilities to build an academic section. A subspecialty interest in adolescent medicine or child abuse is desirable. Submit CV and the names and addresses of five references to: Dr. Dennis Styne, Chair, Pediatrics-2516 Stockton Boulevard, Sacramento, CA 95817. The University of California is an equal opportunity/affirmative action employer. Closes: Open until filled; not later than December 1, 1991 to be considered.

PEDIATRICIAN – Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence E. Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

Faculty Positions

PEDIATRICIAN/PEDIATRIC Infectious Disease specialist – The Division of Immunology and Infectious Disease, Department of Pediatrics, University of Miami School of Medicine invites applications for a position as an assistant professor of clinical pediatrics to provide direct patient care in the pediatrics AIDS inpatient and outpatient units. Potential for involvement in ongoing clinical research protocols. Excellent opportunity for an individual with clinical and teaching skills in the setting of a large county teaching hospital. Training in pediatric infectious disease preferred but not required. Applicants should send a curriculum vitae in confidence to: Gwendolyn B. Scott, MD, Director, Division of Pediatric Immunology and Infectious Diseases (D4-4), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33136. The University of Miami is an affirmative action/ equal opportunity employer.

JUNIOR FACULTY POSITION in the Division of General/Ambulatory Pediatrics is available at Texas Tech University Health Sciences Center, School of Medicine, Lubbock, Texas. Applicant must be board-eligible/-certified. Responsibilities include teaching, patient care and clinical research. Tenure track appointment available to qualified candidates. Call or submit CV to: V.J. Gururaj, MD, Professor, Director Division General/Ambulatory Pediatrics, Texas Tech University Health Sciences Center, School of Medicine, Department of Pediatrics, Lubbock, TX 79430. (806) 743-2266.

CALIFORNIA – The Department of Pediatrics, UCLA School of Medicine, is seeking a neonatologist at the assistant professor level to participate in a program in neonatal medicine at Los Angeles County, Olive View Medical Center. Olive View is an integral part of the UCLA teaching and research program sharing house staff, faculty and facilities. The ability to obtain a California license is required. Applicants should send their curriculum vitae to: S. Douglas Frasier, MD, Chief of Pediatrics, Olive View Medical Center, 14445 Olive View Drive, Suite 3A108, Sylmar, CA 91342. Equal opportunity employer M/F.

THE UNIVERSITY OF CINCINNATI DEPARTMENT OF PEDIATRICS

The University Affiliated Cincinnati Center for Developmental Disorders, a Division of Children's Hospital Medical Center and Department of Pediatrics, College of Medicine, University of Cincinnati, is seeking a pediatrician for the position of Associate Director. Applicants must have completed a fellowship in Developmental Disorders and should qualify for appointment as an Associate or Full Professor. The candidate would be expected to assist the Director in all facets of the program, including administration, teaching, service and research.

UACDD is an interdisciplinary training and service program devoted to the evaluation and care of individuals with a variety of developmental disorders. Seventy-two full-time professional and thirty-nine administrative and support personnel comprise the faculty and staff.

Please send letter of inquiry and a current curriculum vitae to:

**Lusia Hornstein, MD, Professor
Director
Department of Pediatrics/UACDD
Chair, Faculty Search Committee
Pavilion Building
Elland and Bethesda Avenues
Cincinnati, OH 45229**

University of Cincinnati and University affiliated Cincinnati Center for Developmental Disorders are equal opportunity/affirmative action employers.

Faculty Positions

AMBULATORY/GENERAL PEDIATRICS – The Ohio State University Department of Pediatrics and Children's Hospital (Columbus, Ohio) are recruiting board-certified/board-eligible pediatricians into the Section/Division of Ambulatory Pediatrics. The Director of Primary Care, an associate or assistant professor, will play a central role in the reorganization of the pediatric clinics into a private practice model for teaching and patient care. Two additional BC/BE academic primary care positions are also available. It is expected that the successful candidates will be fellowship trained or appropriately experienced, be enthusiastic clinical teachers and have a commitment to clinical research. Additional full- and/or part-time positions are available for BC/BE pediatricians to participate in primary care delivery and clinical teaching in our community outreach programs. University appointment will be at an appropriate rank based on qualifications. Children's Hospital is one of the largest in North America. It is the sole pediatric teaching facility for the Ohio State University College of Medicine. Our primary care programs currently handle more than 45,000 visits annually and are the major ambulatory pediatrics teaching site for pediatric, internal medicine-pediatric and family medicine residency programs as well as medical students from the Ohio State University. Please contact: Lindsey K. Grossman, MD, Chief, Section of Ambulatory Pediatrics, Children's Hospital, 700 Children's Drive, Columbus, OH 43205. (614) 460-8478. The Ohio State University is an AA/EO employer; women and minorities are encouraged to apply.

THE DEPARTMENT OF PEDIATRICS of the University of Pittsburgh and Children's Hospital of Pittsburgh seeks a BC/BE pediatrician at the assistant or associate professor level to join the University Pediatric Diagnostic Referral Service. The position requires an academic generalist preferably with either chief residency experience or general academic pediatric fellowship training. Responsibilities include patient care, teaching, and clinical research, with an emphasis on inpatient care. Rank and salary commensurate with experience. Inquiries should be addressed to: J. Carlton Gartner, Jr., MD, University Pediatric Diagnostic Referral Service, One Children's Place, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-3417. An equal opportunity employer.

DEPARTMENT OF PEDIATRICS, State University New York at Buffalo/Children's Hospital seeks faculty member to join ten member Division of Neonatology. We are seeking a physician with a commitment to pursue research which can be related to perinatal circulatory physiology. We are particularly interested in the responsiveness of and remodeling of the pulmonary vascular bed of the fetus and newborn. Techniques employed could range from integrated physiologic, to isolated organ or tissue, to cellular or molecular. Division conducts NIH-sponsored laboratory research on perinatal pulmonary and circulatory physiology. Clinical research includes six years of experience with surfactant therapy. MD: BE/BC neonatal-perinatal medicine. Assistant or associate professor level. CV to Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. We are interested in identifying qualified minority and women candidates. The State University of New York at Buffalo and the Children's Hospital of Buffalo are affirmative action/equal opportunity employers. No person, in whatever relationship with the University or the Hospital, shall be subject to discrimination on the basis of age, creed, color, handicap, national origin, race, religion, sex, marital, or veteran status.

ACADEMIC PEDIATRIC ONCOLOGIST – The Department of Pediatrics, University of New Mexico School of Medicine, is seeking a BC/BE pediatric oncologist to join an active division of pediatric oncology to share clinical, teaching and research responsibilities. Excellent research opportunities for collaboration with our Cancer Center exist. This is a tenure-line position at the assistant/associate professor level. Send letters of inquiry and CV to: John D. Johnson, MD, Chairman, Pediatrics, University of New Mexico School of Medicine, Albuquerque, NM 87131. Telephone: (505) 272-5551.

NEONATOLOGIST: Director for a 6.5 member community section within the Division of Neonatology of the State University of New York at Buffalo. Using nurse practitioners, the section will provide coverage for a 12-bed Level II Nursery and two Level I Nurseries with a total of 8,500 deliveries. Its members will also rotate through the Level III Nursery and teach fellows, residents and nurse practitioners. The Division of Neonatology currently has ten faculty members and covers a 75-bed Level III Nursery. It conducts NIH sponsored laboratory research and clinical research including six years of experience with surfactant therapy. Contact: Frederick C. Morin III, MD, Chief, Division of Neonatology, Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. (716) 878-7673. Affirmative action/equal opportunity employers.

PHILADELPHIA – Children's Seashore House, a regional pediatric rehabilitation hospital adjacent to and affiliated with The Children's Hospital of Philadelphia, is recruiting a pediatrician trained in developmental pediatrics, chronic diseases or general academic pediatrics, to serve as director of inpatient services. Opportunities are available for pursuit of teaching and clinical research interests. Candidate may be eligible for academic appointment (assistant or associate professor) in the Department of Pediatrics at the University of Pennsylvania School of Medicine. The University of Pennsylvania and the Children's Seashore House are equal opportunity, affirmative action employers. Interested candidates should submit a CV and three letters of reference to: Mark L. Batshaw, MD, Children's Seashore House, 3405 Civic Center Boulevard, Philadelphia, PA 19104. Position is available as of July 1, 1991.

A PEDIATRIC NEUROLOGY residency position is available beginning on July 1, 1992, and we are also considering applicants for 1993, at the Washington University Medical Center in St. Louis, Missouri. This is a three year program designed to educate individuals in the discipline of neurology with special competence in child neurology and with an emphasis on preparing them for an academic career. The clinical settings include Barnes and St. Louis Children's Hospitals. Research experience in diverse areas of neuroscience is available to trainees, many of whom choose to remain for additional research training following completion of their residency. Washington University is an equal opportunity, affirmative action employer. For further information write: Philip R. Dodge, MD, Acting Director, Pediatric Neurology Training Program, Division of Pediatric Neurology, St. Louis Children's Hospital, St. Louis, MO 63110.

INTERMOUNTAIN HEALTH CARE, One of the nation's largest not-for-profit health care systems with 24 hospitals, has practice opportunities available for BE/BC pediatricians in the scenic Intermountain West. Situations range from rural to urban areas and from employment to private practice positions. Work within a premiere health care system and live in beautiful and affordable mountain states with four-season recreational opportunities including skiing, backpacking, hunting, and sightseeing in numerous national parks and forests. Send CV to: Betty Anderson, IHC Physician Services, P.O. Box 57010, Murray, UT 84157-0010. Or call toll-free: (800) 888-3134. Extension 4515.

FLORIDA - Pediatric nurse practitioner wanted to join innovative pediatric practice with comprehensive care center. Reply to: Dr. Robert B. Schultz, Child Health Care Associates, 4415 Sheridan Street, Hollywood, FL 33021. (305) 973-7400.

TENNESSEE — Nashville suburb. BC/BE pediatrician needed for well-established, rapidly growing practice. Beautiful lakeside community with cultural and recreational activities. Close proximity to tertiary care center. Contact: Ken Wyatt, MD, 105 Glen Oaks Boulevard, #102, Hendersonville, TN 37075. (615) 824-1142.

SOUTHERN CALIFORNIA - Established pediatric practice available. Prestige location, \$250,000 gross and growing. Reply to: V. Hemingway, P.O. Box 11792, Costa Mesa, CA 92627.

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P. W. Newacheck, M. A. McManus, H. B. Fox

The Evolution of Surgical Treatment for Congenital Cardiac Disease

J. D. Pigott

The Role of Corticosteroid Therapy in Children With Pneumococcal Meningitis

W. A. Kennedy, M. J. Hoyt, G. H. McCracken, Jr

How Are Pediatric Training Programs Preparing Residents for Practice?

*L. W. Greenberg, P. Getson, C. Brasseux, E. G. Pattishall III, S. Kataria,
G. S. Bartlett, S. B. Tully, D. Shea*

Taurine Decreases Fecal Fatty Acid and Sterol Excretion in Cystic Fibrosis: A Randomized Double-blind Trial

L. J. Smith, F. Lacaille, G. Lepage, N. Ronco, A. Lamarre, C. C. Roy

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American Medical Association

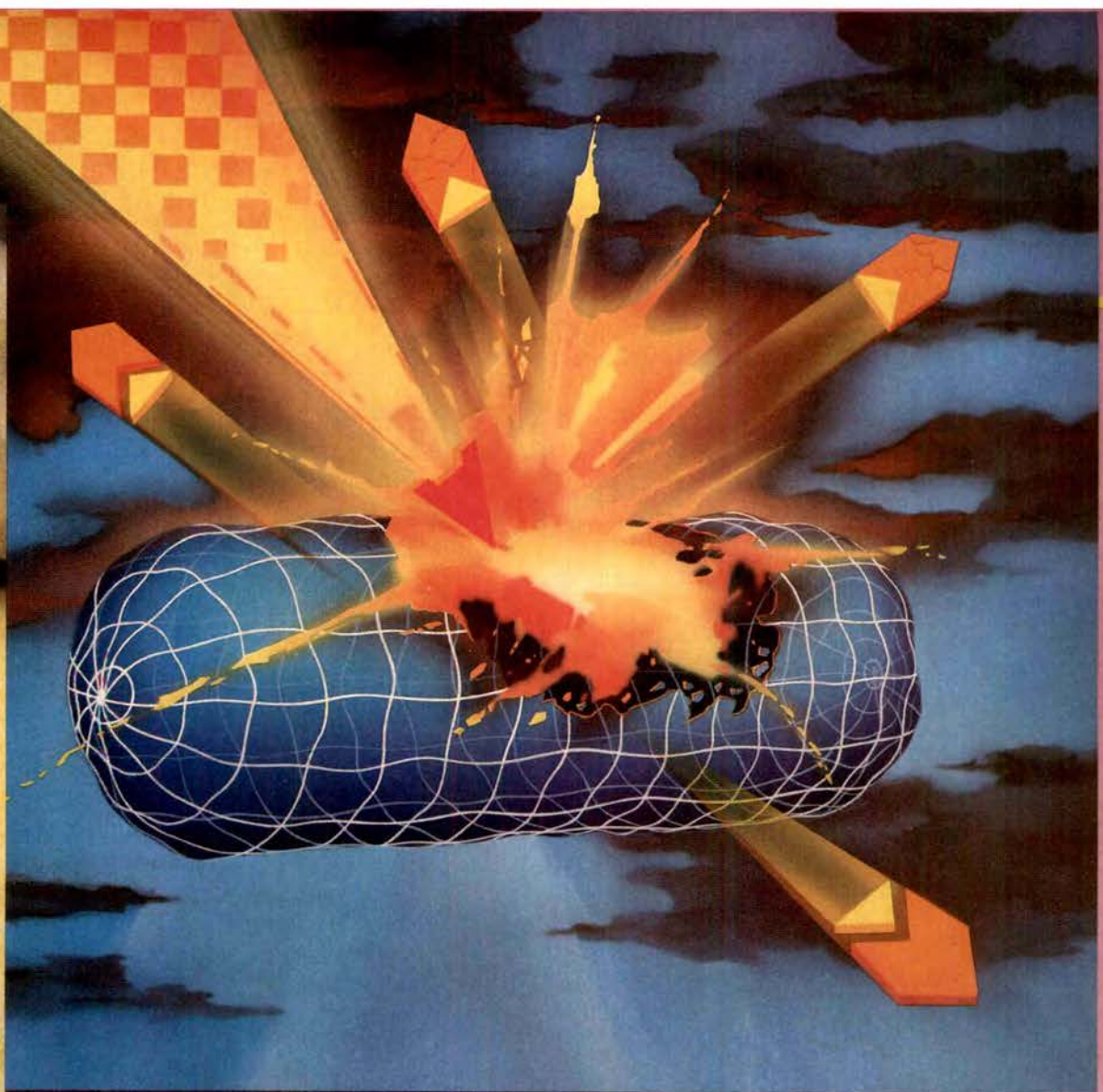
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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower Respiratory Infections caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Branhamella catarrhalis*.

Otitis Media caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Branhamella catarrhalis*.

Sinusitis caused by β -lactamase-producing strains of *Haemophilus influenzae* and *Branhamella catarrhalis*.

Skin and Skin Structure Infections caused by β -lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β -lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β -lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT. INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See Warnings).

Liver: A moderate rise in SGOT, SGPT, AST, and/or ALT has been noted in patients treated with ampicillin class antibiotics including *Augmentin*. The significance of these findings is unknown. As with some other penicillins and some cephalosporins, hepatic dysfunction has been reported rarely, with the predominant effects being cholestatic, hepatocellular or mixed cholestatic-hepatocellular. Signs/symptoms may appear during or after therapy and they resolve completely over time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage: Adults: The usual adult dose is one *Augmentin* 250 tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500 tablet every eight hours.

Since both the *Augmentin* 250 and 500 tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250 tablets are not equivalent to one *Augmentin* 500 tablet. Therefore, two *Augmentin* 250 tablets should not be substituted for one *Augmentin* 500 tablet for treatment of more severe infections.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and other more severe infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Also available as *Augmentin* 125 and 250 chewable tablets.

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THE AMERICAN JOURNAL OF DISEASES OF CHILDREN (ISSN 0002-922X) is published monthly by the American Medical Association, 515 N State St, Chicago, IL 60610, and is an official publication of the Association. Second-class postage paid at Chicago and at additional mailing offices.

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For new applicants, regular registration begins December 2, 1991, and continues through March 2, 1992. The registration fee is \$1050. The registration fee must accompany the completed application material and be *postmarked* by March 2. On December 2, 1991, application material will be sent to qualified residents at their training program addresses. However, any resident who does not receive the material by mid-December should request the material directly from the American Board of Pediatrics.

A three-part partial payment plan will be available for *new* applicants only. The deadline for participation in that plan is January 13; details will be included in the application material. Late registration for new applicants begins March 3. The late registration fee is \$1250, which includes a \$200 nonrefundable late fee. The final deadline for receipt of applications from new applicants is May 1.

In mid-February, reregistration material will be mailed to active candidates who meet the examination requirements. Those who do not meet the examination requirement of having a copy of their permanent, unrestricted license on file will not be sent the reregistration material. Regular reregistration begins February 17 and continues through April 17. Qualified individuals who do not receive the material by March 2 should request the material directly from the American Board of Pediatrics. The reregistration fee is \$950. The reregistration fee must accompany the completed reregistration form and be *postmarked* by April 17. Late reregistration begins April 18. The late reregistration fee is \$1150, which includes a \$200 nonrefundable late fee. The final deadline for receipt of reregistration material is May 1, 1992.

Site assignment is based on the date of receipt of the application or the reregistration material. Seating may be limited at some sites, so early registration is suggested. Correspondence to the American Board of Pediatrics should be sent to 111 Silver Cedar Ct, Chapel Hill, NC 27514-1651 ([919] 929-0461).

Medical Management of Postobstructive Polyuria

Sir.—Obstructive uropathy can be complicated by a defect in urinary concentrating ability that results in marked losses of water and electrolytes after relief of the obstruction. We describe a neonate with posterior

THE PEDIATRIC FORUM

Laboratory Values During Hospitalization*

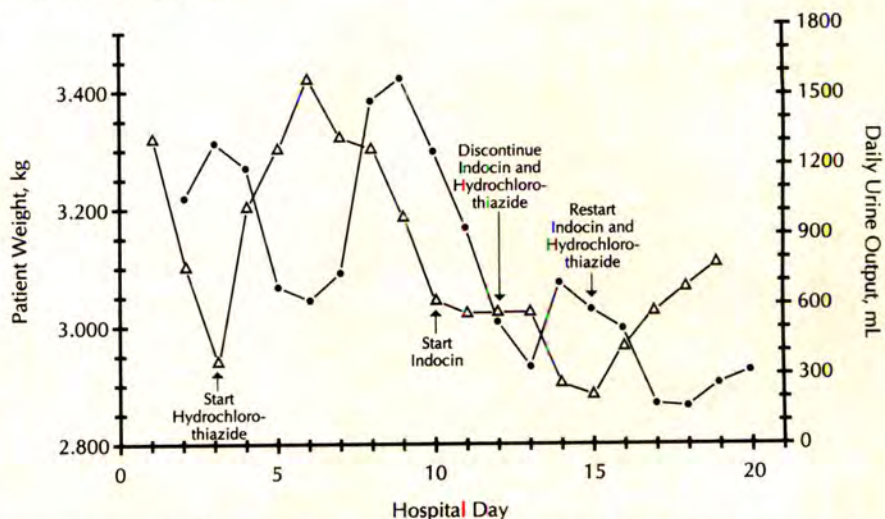
Day of Hospitalization	Sodium, mmol/L	Potassium, mmol/L	Chloride, mmol/L	Bicarbonate, mmol/L	Urea Nitrogen, mmol/L	Creatinine, μ mol/L	Osmolality, mOsm/kg
1	116	5.9	88	9	15	513	110
2	142	4.2	106	15	10	248	110
3	146	5.6	109	20	1.1	44	62
4	138	4.6	99	22	0.4	53	84

*Values for osmolality are from urine; all other values are from serum.

urethral valves who had a marked postobstructive diuresis. Hydrochlorothiazide and indomethacin were used to prevent dehydration. The defect in urine concentration and polyuria recurred on discontinuation of indomethacin and hydrochlorothiazide therapy, but improved after therapy with both drugs was restarted.

Patient Report.—A 6-day-old neonate was admitted for evaluation of abdominal distention, decreased urine output, swelling of the penis and scrotum, and poor feeding, which began 1 day before admission to the hospital. He was born at 37 weeks' gestation by normal spontaneous vaginal delivery after normal pregnancy and labor. He was discharged from the hospital at age 2 days. Results of physical examination showed marked distention and tenderness of the abdomen, with swelling of the penis and scrotum. No abdominal masses were found on palpation. He had poor capillary refill, a blood pressure of 80/50 mm Hg, and a pulse of 140 beats per minute. On admission, serum electrolyte values were as follows: sodium, 116 mmol/L; potassium, 5.9 mmol/L; chloride, 88 mmol/L; (with serum) bicarbonate, 9 mmol/L; urea nitrogen, 15 mmol/L; and creatinine, 513 μ mol/L.

Placing a urinary catheter resulted in increased urine output and prompt improvement of abdominal distention and scrotal swelling. Perfusion and serum electrolyte values improved with intravenous administration of 20 mL of normal saline per kilogram of body weight, followed by intravenous administration of a 0.2% sodium chloride and 0.2% sodium bicarbonate solution. Serum electrolyte concentrations 24 hours after admission were as follows: sodium, 142 mmol/L; potassium, 4.2 mmol/L; chloride, 106 mmol/L; bicarbonate, 15 mmol/L; urea nitrogen (with serum), 18 mmol/L; and serum creatinine, 248 μ mol/L. Urine osmolality was 110 mOsm/kg, and serum osmolality was 301 mOsm/kg. Abdominal ultrasonography study and avoiding cystourethrogram revealed bilateral hydronephrosis; a dilated, thick-walled bladder; a dilated posterior urethra; and bilateral severe reflux. A urine culture yielded a coagulase-positive



Daily weight (triangles) and daily urine output (dot) measured in relation to the use of indomethacin and hydrochlorothiazide.

Staphylococcus, which was treated with intravenous antibiotics.

After 48 hours of urinary drainage and intravenous administration of fluids to replace urinary and insensible fluid losses, the serum creatinine concentration decreased to 44 μ mol/L, and the serum electrolyte concentrations were normal. The Table shows the serum electrolyte, urea nitrogen, creatinine, and urine osmolality values during the patient's initial 4 days in the hospital. Although these values remained essentially unchanged throughout the remainder of the hospitalization, urine output continued to increase, reaching a maximum of 1600 mL/d (21 mL/kg per hour) 9 days after relief of obstruction. This was associated with progressive weight loss and dehydration. Administration of hydrochlorothiazide (1 mg/kg twice daily) to increase proximal tubular reabsorption of sodium and water resulted in only transient improvement in the polyuria until indomethacin (1 mg/kg twice daily) was added (Figure). This led to stabilization of weight and marked reduction in urine output to normal levels (4.8 mL/kg per hour). Discontinuing these medications 2 days later resulted in recurrence of the polyuria in association with weight loss and mild dehydration. Subsequent treatment with indomethacin and hydrochlorothiazide again resulted in a prompt re-

sponse, with a decrease in urine output to normal amounts and stabilization of weight. As mentioned, no changes in serum creatinine or electrolyte values were noted during this time. After 1 week, hydrochlorothiazide therapy was discontinued, and urine output did not increase. After 2 months of normal growth and development (the patient was in the 25th percentile for height and 20th percentile for weight for his age), indomethacin was discontinued, and the polyuria did not recur.

Comment.—A period of postobstructive diuresis often occurs after relief of urinary tract obstruction and this can be associated with a decrease in the ability to maximally concentrate urine.¹⁻⁵ This impairment of the ability to concentrate urine after the initial period of postobstructive diuresis is usually transient, and most patients regain the ability to concentrate urine appropriately days to months after relief of obstruction.^{2,3} A number of factors appear to contribute to postobstructive diuresis. Intravascular volume is often expanded before relief of the obstruction, and a physiologic diuresis would be expected to occur after relief of ob-

struction.⁶ Accumulation of natriuretic factors in response to the volume expansion may also play a role in postobstructive diuresis.⁷ In addition, obstruction results in the accumulation of urea, which may also induce a postobstructive solute diuresis, with large losses of sodium and water.⁸ Finally, there may⁴ or may not³ be a relationship between obstruction complicated by urinary tract infection and impaired ability to concentrate urine. Although data on the relative involvement of each of these factors in humans are lacking, the pathogenesis of postobstructive diuresis is probably multifactorial.

Although there may be multiple defects in distal tubular function, the return of normal function to individual areas of the distal tubule can vary. The ability to maximally concentrate urine, which is a function of the most distal segment of the nephron, should, therefore, also be the most vulnerable to increased intrapelvic pressure.⁹ A group of infants who, after relief of urinary tract obstruction, had an initial defect in aldosterone responsiveness in association with polyuria were studied by Heijden et al.¹⁰ The excessive urinary sodium losses improved in most of the patients, but in some patients polyuria persisted for as long as 10 years after surgical relief of the obstruction. This was thought to be caused by collecting tubule unresponsiveness to antidiuretic hormone.

The clinical findings of polyuria, hypotonic urine, dehydration, and unresponsiveness to administration of exogenous antidiuretic hormone are the hallmarks of nephrogenic diabetes insipidus. This phenomenon may persist for years in some patients with postobstructive nephropathy. Conventional therapy has included sodium restriction and use of thiazide diuretics. This treatment causes a decrease in extracellular fluid volume, which leads to a mild reduction in glomerular filtration rate. As a result, proximal tubular reabsorption of sodium and water is increased, and because less water is delivered to the distal nephron, urine output is reduced.¹ More recently, however, prostaglandin synthetase inhibitors have also been found to be effective in the treatment of hereditary nephrogenic diabetes insipidus¹¹⁻¹⁴ and in

one case of postobstructive acquired nephrogenic diabetes insipidus.²

Prostaglandin synthetase inhibitors may improve renal concentrating ability in patients with postobstructive nephropathy by inhibition of the prostaglandin-mediated suppression of adenylate cyclase and by an antidiuretic hormone-independent mechanism, such as an increase in medullary tonicity.¹¹ By inhibiting medullary prostaglandin synthesis, the inhibitors increase cyclic adenosine monophosphate production by the kidney² and enhance antidiuretic hormone responsiveness.¹⁵ Prostaglandin synthetase inhibitors also increase solute reabsorption in the medullary segment of the thick ascending limb of Henle's loop.¹⁶ This increased sodium reabsorption results in less distal sodium and water delivery, so that fractional free water clearance is reduced, and the urine-plasma osmolar ratio is increased. The net result is a decrease in urine output.¹² Prostaglandin synthetase inhibitors may also decrease glomerular filtration rate and thereby decrease solute delivery to the tubule. It is also possible that increased urea retention plays a role in the antidiuresis associated with the use of indomethacin.¹¹

Several investigators have studied the use of thiazide diuretics and prostaglandin synthetase inhibitors, individually and simultaneously, in the treatment of nephrogenic diabetes insipidus.^{2,11-14,17} Most of these studies involved patients with congenital nephrogenic diabetes insipidus. However, Davidai et al² described the case of a 5-year-old child with posterior urethral valves who had persistent marked postobstructive polyuria (6200 mL of urine excreted per day) with an inability to produce a urine concentration of higher than 59 mOsm/Kg. Treatment with indomethacin corrected the increased urinary excretion of prostaglandin E₂, increased renal adenosine monophosphate production, and resulted in partial improvement in the urinary concentrating defect. Subsequent addition of a thiazide to the treatment regimen restored the child's urinary concentrating ability. The additive effect of thiazides and indomethacin in the treatment of children with congenital nephrogenic diabetes insipidus has also been reported.¹⁴ Although the use of prostaglandin

synthetase inhibitors in children with nephrogenic diabetes insipidus has been previously reported,¹⁸⁻²¹ we could not find reports of their use in neonates with obstructive uropathy.

The response of our patient to hydrochlorothiazide and indomethacin (Figure) demonstrates the effectiveness of this combination in the treatment of postobstructive nephrogenic diabetes insipidus. Initial treatment with hydrochlorothiazide resulted in a transient weight gain and decrease in urine output. However, the addition of indomethacin resulted in stabilization of weight and a marked reduction in urine output. This was not likely due to a decrease in glomerular filtration rate, as the serum creatinine concentration remained stable when indomethacin was added to therapy. Efficacy of therapy was further documented by the recurrence of polyuria and weight loss after discontinuation of the medications and subsequent improvement after reinstitution of therapy.

Few data exist concerning the use of indomethacin and hydrochlorothiazide in neonates with acquired nephrogenic diabetes insipidus. Although no controlled trials regarding the use of indomethacin and hydrochlorothiazide in this setting have been reported, this case demonstrates their effectiveness in the treatment of postobstructive polyuria in neonates. It is unclear whether increased prostaglandin production is the primary cause of this disorder or merely a secondary response to another primary renal insult. However, the use of indomethacin, in combination with hydrochlorothiazide, may be a safe and effective treatment for infants and children with persistent postobstructive polyuria.

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The author would like to thank Bernard S. Kaplan, MBBCh, for his critical review of this article.

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A Third Pattern of Disease Progression in Children Infected With Human Immunodeficiency Virus

Sir.—We read with interest the article by Blanche et al¹ on infants with perinatally acquired human immunodeficiency virus (HIV) infection. We too have noted a bimodal pattern of HIV-related disease in our pediatric patients with acquired immunodeficiency syndrome (AIDS).² In the last few years we have become aware of a third pattern of HIV infection in children, namely, severe manifestations of disease early in life that lessen over the next 5 to 10 years without antiretroviral therapy. This pattern is illustrated in the following patient reports of three HIV-infected children born to drug-abusing mothers.

Patient Reports.—PATIENT 1.—A 10-year-old black twin boy was born between 34 and 36 weeks' gestation. He weighed 1520 g at birth. His Apgar scores were 8/9 at 1 and 5 minutes. The boy had an uncomplicated neonatal course and was discharged after 2 weeks weighing 1950 g. Within his first 10 months of life he had six admissions, two of them prolonged, for diarrhea, dehydration, bronchiolitis, failure to thrive, and developmental delay. He had no opportunistic infections at this time. By age 2 years, the failure to thrive and developmental delay began to improve. By age 4 years, he developed lymphocytic interstitial pneumonia (Centers for Disease Control [CDC] Class P2C) by clinical criteria.^{3,4} At this writing, he had growth retardation, mild

right heart failure secondary to chronic pneumonitis, and infection with *Mycobacterium avium-intracellulare* (his first opportunistic infection), putting him in CDC Class P2D1 as well.⁴ Until recently, the boy attended school with his uninfected twin and did very well. One year he had perfect school attendance.

PATIENT 2.—A 5-year-old black girl had been admitted at age 4 months for pneumonia. No lung biopsy was performed and no pathogen was ever isolated. She responded clinically to empirically administered sulfamethoxazole and trimethoprim. The infant was hospitalized again at age 5 months for vomiting and diarrhea; during this hospitalization she was treated for an *Escherichia coli* urinary tract infection. At age 8 months, she had developmental delay, thrush, hepatosplenomegaly, and lymphadenopathy. At age 9 months, she was hospitalized again for vomiting and diarrhea. She has developed lymphocytic interstitial pneumonitis (CDC Class P2C),^{3,4} but at this writing had no other acute illnesses (aside from otitis media) in the previous four years, and was developmentally normal.

PATIENT 3.—A 3½-year-old black boy was born with a ventricular septal defect. He had congestive heart failure at age 1 month necessitating hospitalization and therapy with digitalis. At ages 6 and 8 months, he was admitted for aseptic meningitis. At age 11 months, he was admitted for pneumonia, at which time he was noted to have diffuse lymphadenopathy. At age 13 months, the boy was admitted for *Salmonella* osteomyelitis of the left shoulder. Lymphadenopathy and thrush were noted during a physical examination. Hemoglobin electrophoresis showed type AA. After being successfully treated for his osteomyelitis, he had no further hospitalizations or serious infections, and at this writing was classified as CDC Class P2A.

Comment.—These cases highlight the difficulty of predicting early in life who among our HIV-infected infants will have the "rapid" form of the disease^{1,2} and who will not. Failure to identify opportunistic infections in these HIV-infected children with multiple hospitalizations under age 1 year appears to be a critical prognostic sign.

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1. Blanche S, Tardieu M, Duliege A-M, et al. Longitudinal study of 94

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In Reply.—We fully agree with the comments by Drs Katz and McNamara regarding the various types of disease progressions in children infected with (HIV). Indeed, some patients with a "borderline" or an unusual progression might not perfectly fit into our description of a "bimodal population" of children according to the progression of the disease.¹ We followed up a child, perinatally infected with HIV, who, at age 4 months, developed *Pneumocystis carinii* pneumonia. Three years later she was well, with no neurologic impairment or secondary infection. Her most recent CD4 cell count was over $1.5 \times 10^9/L$, and the results of her in vitro lymphocyte proliferation tests became progressively normal, showing an association between the clinical and immunologic improvements. In most cases of HIV-infected children, there is a correlation between the severity of the symptoms and the impairment of the immune system or the intensity of the viral load. However, it is more important and useful to show the prognostic value of these tests when performed early in life, before the occurrence of symptoms. Rodgers et al² suggested that the outcome of the disease was worse for children with a positive polymerase chain reaction test for HIV-DNA rapidly after birth, than for those whose polymerase chain reaction test result became positive later in life. However, our experience is slightly different. Finally, more recent techniques such as quantitative DNA polymerase chain reaction, plasma viral culture, and

RNA polymerase chain reaction are under evaluation in infants, and together with the assessment of the immune function, might bring valuable prognostic information. This will become more helpful with the development of treatment protocols in newborns.

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Hydrocele in Kawasaki Disease: Importance in Early Recognition of Atypical Disease

Sir.—Kawasaki disease (KD) is an acute febrile mucocutaneous vasculitis of unknown cause occurring in infants and children.¹ Diagnostic criteria for KD have been defined by the Centers for Disease Control² and are shown in Table 1. In the last decade, cases of atypical KD (AKD) have been reported that do not meet these criteria, but that have a very high coronary artery complication rate and mortality.³⁻¹³ These coronary complications can safely be pre-

Table 1.—Diagnostic Criteria for Kawasaki Disease

Fever for ≥ 5 days
Presence of four of the following five conditions:
Bilateral conjunctival injection
Change(s) in the mucous membranes of the upper respiratory tract, such as reddened pharynx, reddened lips, dry fissured lips, and strawberry tongue
Changes of the peripheral extremities, such as peripheral edema, peripheral erythema, and desquamation
Rash, primarily truncal (polymorphous, but nonvesicular)
Cervical lymph glands ≥ 1.5 cm
Illness unexplained by other known disease processes

vented with intravenous immunoglobulin if administered within 10 days of the beginning of illness.¹⁴⁻¹⁶ In AKD, diagnosis is often delayed, preventing this effective early therapy.³⁻¹³ We report five cases of KD (the first three of which are atypical cases) with development of a hydrocele by 10 days after illness began. To our knowledge, this is the first report of hydrocele with KD, and these findings may aid in early diagnosis and treatment of AKD. The diagnosis of hydrocele was made by the same infectious diseases consultant between 1980 and 1990. During this time, 44 cases of KD were reported at our hospital; 28 occurred in males, six of whom had AKD.

Patient Reports.—PATIENT 1.—A previously well 10-month-old Chinese boy presented with a 4-day history of fever unresponsive to amoxicillin, irritability, and diarrhea, and a 2-day history of truncal rash with perineal accentuation. Initial examination revealed an irritable infant with a temperature of 38.3°C , generalized rash, and shotty cervical lymphadenopathy. Results of the remainder of the examination were normal. Two days after admission to the hospital, an asymptomatic, transilluminating, moderate-sized, noncommunicating hydrocele of the left testicle developed. There was no inflammation or tenderness. Six days after admission, results of an echocardiogram revealed an aneurysm of the left coronary artery. After therapy with intravenous immunoglobulin (400 mg/kg of body weight per day) and aspirin (100

THE PEDIATRIC FORUM

Table 2.—Patient Summary*

Patient No.	Age, mo	No. of CDC Criteria Fulfilled	Day of Illness on Which				ESR mm/h
			Desquamation Occurred	Aneurysm Occurred (Location)	Hydrocele Occurred (Location)	Treatment Was Given	
1	10	2	12	10 (LCA)	6 (left testicle)	10	76
2	11	4	12	8 (LCA)	10 (right testicle)	8	108
3	23	4	13	None	6 (right testicle)	10	23
4	36	5	None	None	7 (left testicle)	7	114
5	44	5	9	None	10 (left testicle)	9	75

*CDC indicates Centers for Disease Control; ESR, erythrocyte sedimentation rate; and LCA, left coronary artery.

mg/kg of body weight per day) was started, fever and mood improved within 24 hours. On day 8 of his hospital stay, periungual desquamation occurred. Follow-up 1 week later showed complete resolution of the hydrocele.

PATIENT 2.—A previously well 11-month-old white boy presented with a 5-day history of a rectal temperature of up to 40.8°C and generalized rash with perineal accentuation. He was irritable and anorexic. He had a mild cough and clear rhinorrheal discharge for 3 days. Results of initial examination revealed an irritable infant with a temperature of 39.2°C, non-exudative pharyngitis, truncal rash, palmar erythema, and foot edema. Results of the rest of the examination were normal. Results of an echocardiogram on day 3 of hospitalization revealed proximal left coronary artery dilatation of 4.0 mm. Administration of intravenous immunoglobulin (400 mg/kg of body weight per day) and aspirin (100 mg/kg of body weight per day) was followed by resolution of fever and improved mood by the next day. Five days after admission to the hospital, a transilluminating, small, non-communicating hydrocele of the right testicle developed that was not present on admission; this hydrocele was asymptomatic and nontender, with no inflammation. On day 7 of the hospital stay, periungual desquamation occurred. Follow-up 1 week later showed complete resolution of the hydrocele.

PATIENT 3.—A 23-month-old white boy presented with a 6-day history of a temperature of up to 39°C, unresponsiveness to amoxicillin, and generalized rash, and a 2-day history of red, cracked lips and red eyes. Results of initial examination revealed a febrile child with a temperature of 39.4°C, clear rhinorrheal discharge, bilateral nonexudative conjunctivitis, erythematous cracked lips, strawberry tongue, generalized rash with perineal accentuation and desquamation, and a transilluminating small hydrocele of the right testicle. The hydrocele was noncommunicating and asymptomatic, with no inflammation. Results of an echocardiogram were normal. The pa-

tient's temperature returned to normal after intravenous immunoglobulin (400mg/kg of body weight per day) and aspirin (100 mg/kg of body weight per day) were administered on day 4 of hospitalization. Periungual desquamation occurred on day 7 of the hospital stay. Records from hospital admissions at ages 5, 6, and 12 months and a parental report of the child's health history did not reveal hydrocele. On 2-week follow-up, the hydrocele had resolved.

PATIENT 4.—A previously well 3-year-old American Indian boy presented with a 7-day history of fever, cervical lymphadenopathy with tenderness, red eyes, red tongue, and arthralgias. He was unresponsive to amoxicillin, which was substituted with erythromycin ethylsuccinate and sulfisoxazole after development of a generalized rash. Results of initial examination revealed a temperature of 38.6°C; bilateral nonexudative conjunctivitis; dry, erythematous cracked lips; a red tongue; bilateral cervical lymphadenopathy with tenderness; indurated edema of the hands and feet; a desquamating perineal rash, and a transilluminating small hydrocele of the left testicle (which had not occurred previously by parental report). The noncommunicating hydrocele was nontender, with no inflammation. Results of an echocardiogram were normal. Treatment with intravenous immunoglobulin (400 mg/kg of body weight per day) and aspirin (100 mg/kg of body weight per day) on admission resulted in resolution of fever the next day. Results of a follow-up examination revealed complete resolution of the hydrocele.

PATIENT 5.—A previously well white boy aged 3 years 8 months presented with a 7-day history of fever that was unresponsive to amoxicillin and a generalized rash. For 4 days before admission to the hospital, he had red eyes and a red tongue. Results of initial examination revealed a rectal temperature of 39.5°C, irritability, bilateral nonexudative conjunctivitis, strawberry tongue, rash, and hepatomegaly. Results of the rest of the examination were normal. Periungual

desquamation occurred on day 2 of hospitalization, and a transilluminating moderate-sized hydrocele of the left testicle developed on day 4. The hydrocele was communicating, and asymptomatic with no inflammation. Results of an echocardiogram were normal. He was treated with aspirin (100 mg/kg of body weight per day) on day 2 of hospitalization, with resolution of the fever by day 5. The hydrocele was surgically excised 2 years later.

Other diagnoses were excluded for these patients based on negative results of the following tests (if indicated): complete blood cell count; urinalysis; lumbar puncture; bacterial cultures of blood, urine, throat, and cerebrospinal fluid; viral cultures of stool, throat, nasopharynx, and cerebrospinal fluid; viral serologic tests, including the monospot test; antistreptolysin-O titer; tests to identify antinuclear antibody and rheumatoid factor; chest roentgenogram; abdominal ultrasound; and measurement of immunoglobulins.

Comment.—Although initially thought to be a benign febrile illness in children,¹ KD has been found to have significant complications, a mortality rate of up to 2%,¹ and a coronary artery aneurysm or ectasia rate of 15% to 25%.¹⁵ Most of these coronary dilations have resolved on follow-up angiography and echocardiography, but vessel wall abnormalities often persist^{17,18}, the ultimate fate of patients with these coronary abnormalities, including risk for future ischemic heart disease, is unknown.¹ In fact, there are several reports of myocardial infarction or sudden death months to years after an illness suggestive of KD.¹⁹⁻²⁵ Administration of intravenous immunoglobulin combined with high-dose salicylate therapy is known to significantly decrease the coronary complication rate.^{14,15} The ultimate long-term benefits of this therapy are yet to be defined.¹⁶ No published studies have been conducted that suggest a benefit

of therapy if begun after the 10th day of illness.¹⁴⁻¹⁶

In the last decade, there have been many reports of KD that does not satisfy the diagnostic criteria of the condition, but that are complicated by a high rate of coronary abnormalities (90%) or mortality (35%).³⁻¹³ In most of these atypical cases, diagnosis was made late in the disease process, when results of echocardiography or autopsy revealed coronary dilatation or aneurysm. For effective early intravenous immunoglobulin therapy in these cases, diagnostic clues before the 10th day of illness are needed. Reported herein are five patients (Table 2) with KD in whom hydrocele developed by day 10 of illness. The first three patients had AKD. In all but one patient, there was complete resolution of hydrocele within 2 weeks of the acute illness. To our knowledge, the finding of hydrocele in KD has not been previously reported. A possible mechanism for development of hydrocele is suggested by reports of a high incidence of spermatic cord and testicular arteritis discovered at autopsy of subjects with KD.²⁶⁻²⁸

In 1976, Tanaka et al²⁶ reported testicular arteritis in five (23%) of 22 autopsies of subjects with KD and in four (36%) of 11 autopsies of infants with KD. Infantile periarteritis nodosa and KD are now considered the same disease,^{26,28-30} and studies of infantile periarteritis nodosa have reported a high incidence of testicular or spermatic cord arteritis at autopsy: three (25%) of 12 in a 1963 review²⁷ and nine (60%) of 15 in a 1977 review.²⁸ The 1977 review by Landing and Larson reported hydrocele in eight (75%) of 12 infants with infantile periarteritis nodosa.²⁸ In fact, in Henoch-Schönlein purpura³¹ and classic adult polyarteritis nodosa,³² testicular arteritis is not uncommon, and hydrocele has been reported with these conditions. This may be a sympathetic effusion resulting from the underlying arteritis inflammation.

Although the finding of hydrocele in KD needs to be confirmed in prospective studies, we suggest that development of a hydrocele during an acute febrile illness is suggestive of KD, and that identifying hydrocele may aid in the early diagnosis and effective treatment of KD. Hydrocele is a particularly useful sign of possible dis-

ease in infants with atypical presentations of Kawasaki disease.

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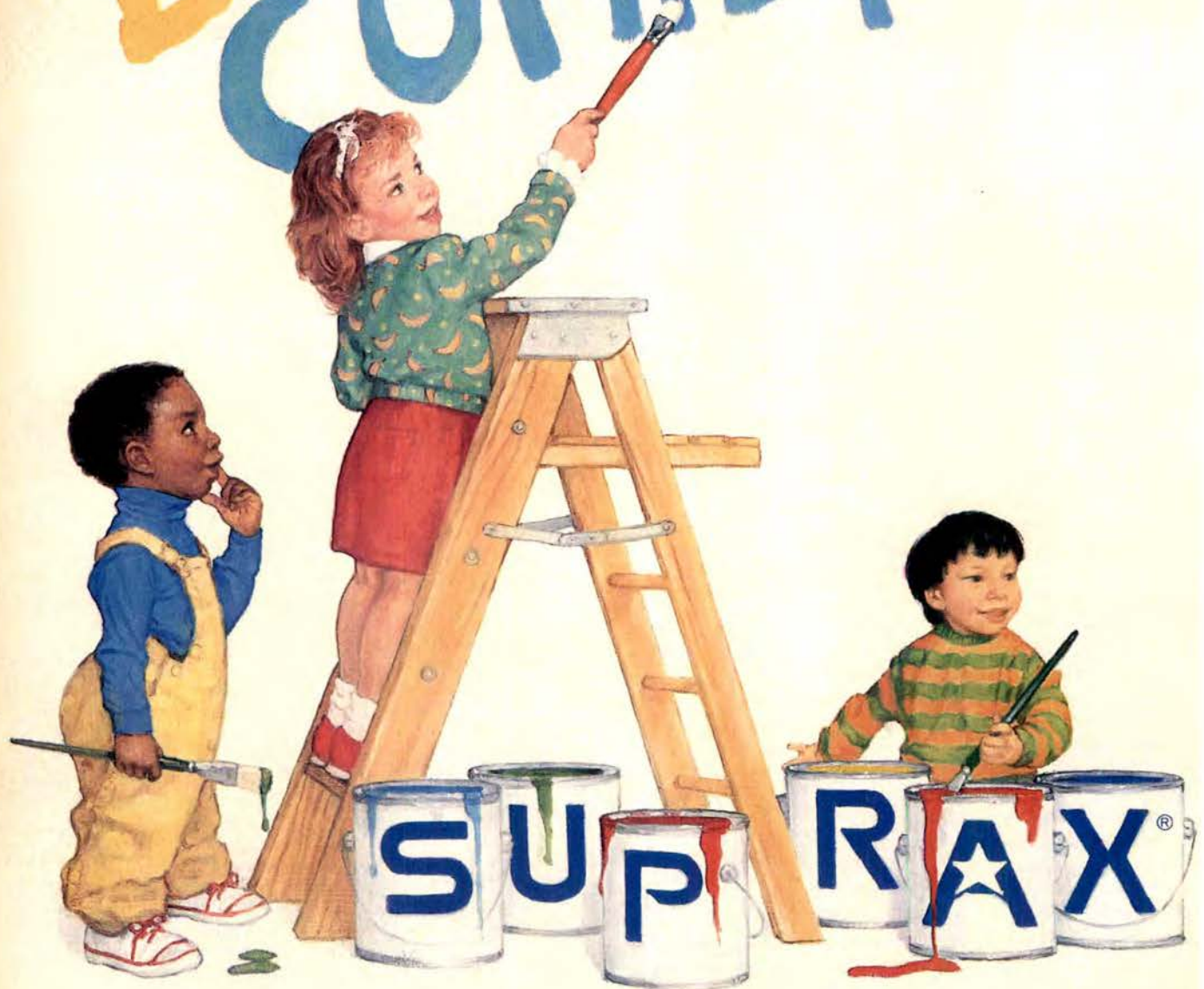
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THE RIGHT COMBINATION OF

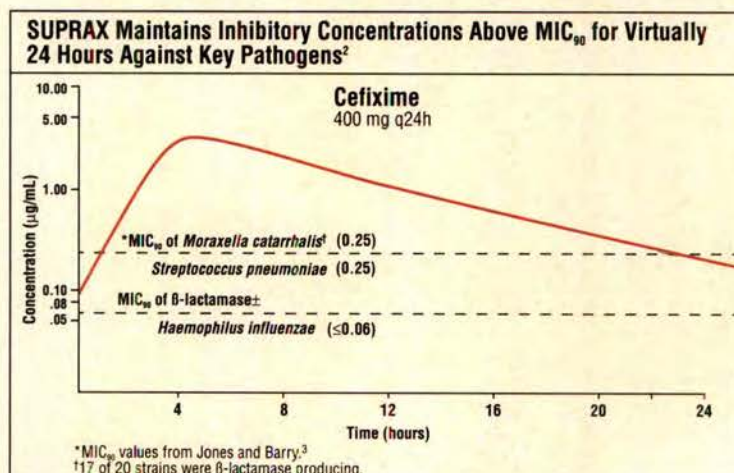
**ACTIVITY
EFFICACY
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ADVANTAGES FOR OTITIS MEDIA*

Activity

- Excellent activity against β -lactamase producing pathogens^{†1}



Efficacy

- Outstanding clinical success noted in clinical trials and confirmed in 20,000-patient study⁴

Compliance

- Better compliance because of convenient qd dosing⁵
- Great strawberry taste—rated #1 for taste⁶

ONCE-A-DAY
SUPRAX[®]
cefixime/Lederle
Oral Suspension 100 mg/5 mL
8 mg/kg/day

***The right combination of advantages
in one antibiotic***

*Due to indicated susceptible organisms.

[†]Although a useful guide, *in vitro* activity does not necessarily correlate with clinical response.

Cephalosporin antibiotics should be administered cautiously in penicillin-sensitive patients, as partial cross-allergenicity for these two drug classes has been reported. SUPRAX is contraindicated in patients with known allergy to the cephalosporin group of antibiotics. Please see complete Prescribing Information for WARNINGS, ADVERSE REACTIONS, and CONTRAINDICATIONS. GI side effects are the most frequently reported adverse effect.

SUPRAX is administered as a single dose, once a day, or if preferred, in equally divided doses twice a day.

Please see brief summary of Prescribing Information on adjacent page.

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 8 mg/kg/day

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Brief Summary

SUPRAX® Cefixime

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

Otitis Media caused by *Haemophilus influenzae* (beta-lactamase positive and negative strains), *Moraxella (Branhamella) catarrhalis* (most of which are beta-lactamase positive), and *Streptococcus pyogenes*.

Note: For information on otitis media caused by *Streptococcus pneumoniae*, see **CLINICAL STUDIES** section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S. pneumoniae* and *H. influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are known.

Pharyngitis and Tonsillitis caused by *S. pyogenes*.

Note: Penicillin is the usual drug of choice in the treatment of *S. pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by *Escherichia coli* and *Proteus mirabilis*.

*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, *S. pneumoniae* was isolated from 47% of the patients, *H. influenzae* from 34%, *B. catarrhalis* from 15%, and *S. pyogenes* from 4%.

The overall response rate of *S. pneumoniae* to cefixime was approximately 10% lower and that of *H. influenzae* or *B. catarrhalis* approximately 7% higher (12% when beta-lactamase positive strains of *H. influenzae* are included) than the response rates of these organisms to the active control drugs.

In these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated 2 to 4 weeks posttreatment, but persistent infection was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs (18% including those patients who had *H. influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the 2- to 4-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at 2- to 4-Weeks Posttherapy
 Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime(a) 4 mg/kg bid	Cefixime(a) 8 mg/kg qd	Control(a) drugs
<i>Streptococcus pneumoniae</i>	48/70 (69%)	18/22 (82%)	82/100 (82%)
<i>Haemophilus influenzae</i> beta-lactamase negative	24/34 (71%)	13/17 (76%)	23/34 (68%)
<i>Haemophilus influenzae</i> beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1(b)
<i>Moraxella (Branhamella)</i> <i>catarrhalis</i>	26/31 (84%)	5/5	18/24 (75%)
<i>Streptococcus pyogenes</i>	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

(a) Number eradicated/number isolated.

(b) An additional 20 beta-lactamase positive strains of *H. influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins.

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild

SUPRAX® Cefixime

cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuation, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be excluded.

PRECAUTIONS

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis. (See **DOSAGE AND ADMINISTRATION**.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferrocyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinistix®,** Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix®** or Tes-Tape®**).

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Use in Pregnancy: Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontinuing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (3.8%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets.

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued. Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events.

Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous colitis were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy.

Hypersensitivity Reactions: Skin rashes, urticaria, drug fever, and pruritus. Erythema multiforme, Stevens-Johnson syndrome, and serum sickness have been reported rarely.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase.

Renal: Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Prolongation in prothrombin time was seen rarely.

Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION** and **OVERDOSAGE**). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytopenia, neutropenia, agranulocytosis.

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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"Grampa, Can I Get Something That I'd Like?"



William B. Strong, MD

G“Grampa, can I get something that I’d like” hit me like a Mike Tyson uppercut to the solar plexus. The sports metaphor is intentional. I enjoy sports participation more than as a spectator.

Max is my grandson; he’s only age 4½ years. He knocked me out in Toys “R” Us with the above question. I rarely see my daughter Beth and her three children since they live in New Hampshire. This past April, I was really looking forward to seeing them. I dreamt and fantasized about how much fun we were going to have playing together. Until now, it’s been mainly with blocks and Legos. Legos are my favorite. Well, it was spring and I thought it would be fun to play catch and bat a ball with Max and Caroline, his sister. Will is still a bit young for baseball; he’s only age 18 months. So, after I arrived for my 2-day visit and settled in, I inventoried all the kids’ toys. No baseball paraphernalia! It was time to go to Toys “R” Us for some baseball gloves and a tee-ball set. Boy! Were we going to have fun! Grampa was in hog heaven. “Max, how’d you like this glove?” “What about you, Caroline?” “What color ball should we get?” “We need a light bat so nobody gets hurt.” It hap-

pened after we (I) made some super selections and were headed toward the sales counter. That’s when Max chopped me down. Trailing on my left side, he threw a sneak punch. POW! It took a moment for me to catch my breath, to get my defenses up. But what defense is there for a little boy who innocently looks up at you and asks “Now grampa, can I get something that I’d like?” What a fantastic lesson; one that I espouse every day as a pediatrician, but was blinded by my own selfish desires. Sure, I wanted these for the children. STOP! Examine that last sentence. It began “I wanted,” not what Max and Caroline wanted. All Max wanted was a little truck. Max got his truck and I got an incredible lesson, and one that I hope I never forget. Thanks, Max.

I do not believe this little vignette is a unique experience. How often do we do for others what we would want them to do for us rather than doing for them what they want to be done for them?

THE PEDIATRIC FORUM

Tiny Tim Remembered

Sir.—Of all the haunting images that moved the hardened heart of Ebenezer Scrooge on that infamous Christmas Eve, the picture of Tiny Tim seemed to touch him most deeply. Tiny Tim, perhaps the most pathetic yet endearing character in Dickens’ story, *A Christmas Carol*, suffered from a crippling condition. “Alas for Tiny Tim, he bore a little crutch and had his limbs supported by an iron frame.” Sitting by the fire after Christmas dinner, Bob Cratchit held Tim’s “ . . . withered little hand in his, as if he loved the child, and wished to keep him by his side, and dreaded that he might be taken from him.”

Dickens has little more to say about the boy’s illness. Tim might have had any one of a number of congenital abnormalities of his limbs. In an age before corrective surgery and prosthesis, he was likely destined to remain a cripple for life. Tiny Tim’s condition, however, was more serious. The Ghost of Christmas Present observed to Scrooge: “I see a vacant seat in the poor chimney corner, and a crutch without an owner carefully preserved. If these shadows remain unaltered by the Future, the child will die.” Even the most casual Dickens reader must occasionally wonder about the nature of this crippling, eventually fatal disease.

In 1843, when Dickens wrote *A Christmas Carol*, approximately one half of the English population was affected with tuberculosis. It was the single greatest cause of death and disease in the western world.¹ It was particularly common among families of the lower classes. Tuberculosis tended to pass from one generation to the next in families during the winter months when the house was closed against the cold and parents huddled with their children for warmth.¹ It is possible that Bob or Mrs Cratchit had tuberculosis, and passed it on to Tiny Tim, who developed a pulmonary infection initially. He may have experienced hematogenous spread because of malnutri-

tion and altered immunity. (It was not easy to feed a family of eight on 15 "bob" a week.) Bone and joint complications accompany primary pulmonary tuberculosis in as many as 5% of children, according to a relatively recent review.² It is easy to imagine that these complications occurred more commonly 150 years ago.

Tuberculous spondylitis was first described by Percivall Pott in 1779.³ The thoracic vertebrae are the most commonly affected, and the majority of cases in children occur between the ages of 3 and 10 years.⁴ Patients experience pain and stiffness, followed by wasting, fatigue, and fever. Degeneration of the spine leads to shortened trunk height as the ribs descend into the pelvis, perhaps the reason Tim was "Tiny."⁴ Paraplegia accompanies tuberculosis of the spine, with involvement of the midthoracic vertebrae in as many as 25% of patients.⁴ Death occurs if the tuberculosis abscess ruptures through the dura and drains into the spinal canal.⁴

Tiny Tim did not die, because Scrooge changed his ways and became "a second father" to him. Ebenezer could have paid for Tiny Tim to be moved to a sanatorium like the "Royal Sea Bathing Infirmary for Scrofula" in Margate, England, which was started in 1791.¹ There, Tiny Tim would have enjoyed good hygienic conditions, rest, and adequate nutrition and recumbency in the fresh salt air. He would have been fitted with a custom fixative apparatus such as the Davis spinal assistant.⁵ Thus, he would have recovered some of his leg function and experienced remission of his disease.

There are many possible causes for Tiny Tim's affliction. Other forms of hematogenous osteomyelitis or septic arthritis can cause a crippling fatal condition. Diseases such as these, however, cause a child to be acutely ill, and hardly energetic enough to accompany his father to church as Tim did that Christmas. A myelomeningocele could cause a crippling condition like the one that affected Tiny Tim. Death in a child with this defect could result from urosepsis—a complication of a neurogenic bladder—or from erosion of the skin

above the defect, and meningitis. Leukemia with bone involvement could lead to a crippling, fatal condition. One expects the victim to appear more sick than Tim. In the case of this malignancy, one also has to assume that Tim experienced a spontaneous remission after Scrooge's reformation.⁶

Nutritional deficiencies represent another group of possible causes for Tiny Tim's malady. Scurvy, a deficiency of vitamin C, might account for his symptoms. This deficiency, first described by Sir Thomas Barlow in the late 19th century, causes painful, swollen legs, pseudoparalysis, fractures of the epiphyseal plates, weakness, lethargy, and arthralgias. Children with scurvy may also have visceral and oropharyngeal bleeding. Death may occur after cerebral hemorrhage.⁷ The patients described by Barlow were younger than Tim, between 6 and 15 months of age in most instances.⁷ More importantly, scurvy did not occur in the very poor, since potatoes were a major source of dietary starch.⁷ Potatoes were a part of the Cratchits' diet. They feasted on goose, apple sauce, and potatoes that Christmas Eve. Without a doubt, this meal was better than their average daily fare. However, only one medium-sized potato a day is required to prevent the clinical manifestations of scurvy.⁸

Tiny Tim could also have suffered from vitamin D-deficient rickets. The burning of fossil fuels during the 19th century blackened the skies over European and American cities. Air pollution filtered out the sunlight and caused epidemic rickets.⁶ In the most advanced stages, rickets can cause deformity of the thoracic cage, such as pigeon breast and kyphoscoliosis, as well as bowed legs, knock-knees, and coxa vara. Even when severely affected, children with rickets are usually not crippled; and rickets alone would rarely be fatal.⁹

Tuberculosis was common in Dickens' England. Many of his contemporaries suffered from the disease. In literature, it was pictured as a tragic yet romantic, gradually wasting process that affected rich and poor alike. The prevalence of tuberculosis and its popularity as a literary theme may have influenced Dickens' portrayal

of Tiny Tim's affliction.¹

One hopes that a physician of this decade would never allow Tim's condition to progress to such an advanced state. Tuberculosis would be suspected if this sickly, anergic boy with pneumonia were referred to a medical center. The diagnosis would be made quickly by gastric lavage and Ziehl-Neelsen stain, or bronchoalveolar lavage with tuberculo-tearic acid assay, before the onset of secondary hematogenous spread. The incidence of tuberculosis is on the rise, especially in areas of poverty. The practitioner of today would do well to heed the words of a somber Bob Cratchit: "I am sure we shall none of us forget poor Tiny Tim, shall we?"

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The opinions expressed by the author are not to be construed as being official or as reflecting the views of the Department of the Army or the Department of Defense.

I thank Howard Panitch, MD, and Daniel Schidlow, MD, for their assistance with the manuscript.

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Cautionary Note on the Use of Empiric Ceftriaxone for Suspected Bacteremia

Empiric use of parenteral ceftriaxone sodium is becoming increasingly prevalent in the treatment of suspected occult bacteremia in young, highly febrile children who lack an apparent focal infection other than presumed viral upper respiratory tract infection. This strategy has begun to pervade clinical practice in the absence of any published data to prove its efficacy. The authors of two recent exercises in decision analysis conclude that empiric antimicrobial therapy is the most cost-effective and clinically beneficial treatment strategy and recommend its use.^{1,2} We write to express concern and urge caution in adopting this approach lest it further complicate the difficult task of treating occult bacteremia by requiring a more extensive evaluation and generating a potentially ambiguous database.

Occult bacteremia is a relatively common problem in pediatric patients, occurring most often in children between ages 3 and 36 months with temperatures of at least 38.9°C. Numerous reports have identified an incidence of bacteremia in approximately 3% to 6% of patients from both the private and public sectors.³⁻⁵ By far, the most common bacterial species associated with occult bacteremia is *Streptococcus pneumoniae*. Much less frequently, *Haemophilus influenzae* type b and *Neisseria meningitidis* are implicated. Young age and high fever are risk factors for bacteremia. The presence of various clinical or laboratory features, such as seizures or elevated sedimentation rate or white blood cell count, may further increase the likelihood of bacteremia. However, no single feature or combination of clinical or laboratory parameters identifies all

patients with bacteremia at the time of initial presentation. Accordingly, some authorities have made the controversial recommendation to routinely obtain blood cultures from all children at risk for occult bacteremia in the hope of achieving an early diagnosis.⁶

The outcome of patients with occult bacteremia is influenced by a number of factors, including the host, the pathogen, and perhaps the empiric initiation of antimicrobial therapy. In many patients, bacteremia clears spontaneously; in others, a focal infection, such as otitis media or pneumonia, develops within the next 24 to 48 hours, thereby directing the initiation of specific therapy in an acceptably timely fashion. Some patients remain persistently bacteremic while others develop serious focal infections, including meningitis, the latter approximately 4% of the time.⁷ The prime rationale for empirically treating all patients with suspected occult bacteremia is prevention, if possible, of this most serious complication—meningitis.

This leads us to ask two questions: (1) Are blood cultures essential in treating patients with suspected occult bacteremia? (2) Will empiric therapy successfully prevent the development of serious complications of bacteremia? Review of medical records of patients with occult bacteremia seen at the Yale-New Haven (Conn) Hospital showed that nine of 21 patients with serious focal complications or persistent bacteremia returned to the emergency department because of continued symptoms and signs before notification about positive blood cultures.⁸ Furthermore, a study regarding the usefulness of blood cultures employing decision analysis technique implied

that a "no blood culture" strategy had the highest utility.⁹ Accordingly, argument can be made for the treatment of patients at risk for occult bacteremia without obtaining blood cultures at the first encounter; when feasible, careful follow-up and comprehensive reevaluation of patients who fail to improve under observation are a viable and perhaps preferable alternative.

Data addressing the success of empiric therapy in preventing serious complications of bacteremia are scant. The results of a recently published study, which prospectively evaluated oral antimicrobial therapy in the treatment of suspected bacteremia, were disappointing.¹⁰ Only modest benefits in terms of fever reduction and clinical improvement were associated with presumptive therapy. Major infectious morbidity was not averted in the children who received antibiotic therapy.

Will ceftriaxone sodium be effective in preventing meningitis if it is used empirically in patients with presumptive bacteremia? On the basis of limited clinical data,^{11,12} we presume that one or two doses of ceftriaxone will produce a serum level sufficient to sterilize the bloodstream of *S pneumoniae*, *H influenzae* type b, and *N meningitidis*, and to prevent seeding of the meninges in most patients. It is likely that empiric therapy would also sterilize a recently inoculated cerebrospinal fluid, although such a regimen may not suffice to adequately treat established meningitis. The significant potential benefit achieved by parenteral ceftriaxone in patients with occult bacteremia would be the elimination of four cases of meningitis among every 100 patients with occult bacteremia.

Realizing such a benefit would require the treatment of 2500 patients with suspected occult bacteremia. Nevertheless, a decision regarding the routine use of parenteral ceftriaxone in patients at risk for occult bacteremia requires a balanced consideration of potential problems as well as benefits.

Aside from the obvious potential liabilities associated with treating large numbers of nonbacteremic patients with an antibiotic (eg, allergic, idiosyncratic, or other adverse reactions), other important adverse consequences are associated with the strategy of presumptive therapy. If physicians elect the routine empiric treatment of young children with suspected bacteremia (ie, all infants and children between ages 3 and 36 months with a temperature of at least 38.9°C), they would be appropriately expected to obtain blood and urine cultures (the latter by suprapubic aspiration or catheterization) from all such patients before initiating treatment. A lumbar puncture would also be required for any patient whose clinical status mandated excluding a diagnosis of unsuspected early meningitis before antibiotics were given. If a blood culture is reported to be positive, it will be necessary to obtain another blood culture and, frequently, to repeat lumbar puncture to assess whether bacteremia had resolved and whether an occult, partially treated meningitis had developed. Although the routine use of blood cultures is a controversial issue, using ceftriaxone sodium as empiric therapy mandates the necessity of obtaining blood cultures (generating laboratory costs and patient discomfort) and subjects many bacteremic infants and children treated in this way to at least one, or in some cases two, lumbar punctures.

Some patients with suspected occult bacteremia will be initially reported as having blood cultures containing "gram-positive cocci." Approximately 40% to 50% of these isolates will prove to be contaminants.^{3,13} Many of these gram-positive cocci will ultimately be identified as coagulase-negative staphylococci and, as such, will be eventually dismissed as contaminants. However, patients will fre-

quently be recalled to the hospital, have blood cultures repeated, and be hospitalized for parenteral therapy of presumed serious infection until the identity and significance of the blood culture isolates are clarified. Occasionally, *Staphylococcus aureus* will be isolated. Unfortunately, in such instances, it may not be possible to clarify the significance of such an isolate simply by repeating the blood culture. If the second blood culture is sterile, it may be unclear whether the original isolate represents a contaminant or a partially treated pathogen. In some such circumstances, bone scans or echocardiograms will be performed to locate presumed staphylococcal infection. Furthermore, when blood cultures prove to be positive and patients are subsequently recalled to the hospital, it puts us in the somewhat paradoxical situation of admitting the "well" child to the hospital after having sent the "sick" child home 24 hours earlier. If presumptive therapy had not been used in such children, decisions concerning treatment would have been based on clinical appearance, without concerns about the confounding impact of partial therapy.

Another dilemma will unfold when a patient whose blood culture is negative returns 24 hours after having received parenteral ceftriaxone looking sicker or unimproved. According to a recent study, there may be a 50% risk of failing to detect bacteremia when only a single blood culture is obtained.¹⁴ Unfortunately, the value of a repeated blood culture done at this time will have been obviated by the prior partial treatment. Equally problematic is the situation in which the initial urine culture is reported to contain two or three bacterial species or a colony count of ambiguous significance. Although contamination of urine specimens obtained by suprapubic aspiration or catheterization is infrequent, "clean-catch" or "bagged" specimens are more likely to have been obtained for culture when clinical suspicion of urinary tract infection is relatively low. Again, a repeated urine culture will be of little value in clarifying the situation because the ceftriaxone will surely have eradicated a true pathogen or obscured a contami-

nant. The significance of the bacteriuria cannot be established and the need for radiographic evaluation of the urinary tract will be difficult to determine. Again, had presumptive therapy been withheld, the database could easily have been clarified.

Philosophically, the most troublesome aspect of the routine use of empiric ceftriaxone for suspected occult bacteremia is that it may lead to a less thoughtful approach to treatment of the patient. Until now, we have individually considered the disposition of patients at risk for occult bacteremia. When particularly worried (when sepsis seemed a more likely possibility), we have hospitalized such patients for observation or presumptive treatment until laboratory results became available. In those few patients, the "complete" sepsis evaluation was properly undertaken (including suprapubic bladder aspiration or urethral catheterization) and easily justified. In the remaining febrile children, we used carefully scheduled follow-up, often without blood culture, to ensure further clinical and laboratory evaluation as individually warranted. The current availability of a powerful, broad-spectrum, long-acting antimicrobial agent should not tempt us to adopt strategies based on the routine use of an unproved therapy, which may further complicate the treatment of febrile children, who, for the most part, are not bacteremic.

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Adolescents With Chronic Illness

The article by Newacheck et al in this issue of *AJDC* improves our understanding of the epidemiology and prevalence of chronic illness in adolescence and defines some of the physical limitations and behavioral consequences of chronic illness. A striking finding is the apparently high rate of chronic illness in this age group, approaching one in three adolescents aged 10 to 17 years. Data available in this study do not allow determination of the physiological severity of these chronic conditions; however, other studies^{1,2} suggest that about 10% to 20% of children with chronic illness have severe conditions of the type likely to have a daily impact on the child's life.

Thus, the data presented in the article by Newacheck et al suggest that 3% to 6% of adolescents have severe long-term illnesses, consistent with other work indicating similar rates of health disability among adolescents.³ Of great import is the finding that these rates are similar to those for younger children (using the same data set) and that most of these chronic health conditions are compatible with long life. Thus, the very large majority of adolescents with chronic illnesses will survive to adulthood, and one can predict similar or even higher rates of chronic illness among young adults. The secondary physical and behavioral problems faced by adolescents with chronic illness, as described by

Newacheck et al, may have as great an impact on their ability to function as adults as does their primary health condition.

As the authors point out, adolescence is a time of great stress made more difficult by the presence of a chronic health condition. Although adolescents face many complex tasks, two merit special attention for adolescents with chronic illnesses: the development of autonomy and formation of personal identity. Chronic illnesses often create special dependency needs, such as physical therapy for the person with arthritis or cystic fibrosis and help with pulmonary toilet for a person dependent on a respirator or with a tracheostomy. Developing satisfactory autonomy in the context of maintaining significant physical dependency can be very difficult for many adolescents. Further, the tendency of parents and clinicians alike to label children by their disease (eg, "diabetics," "cystics," or "leukemics") often allows the disease, its consequences, and treatments to obscure the underlying child or adolescent. For some, the disease becomes their identity.

Exclusive attention to the disease limits attention to other areas important to adolescence (eg, growth and physical development, sexuality, athletics, and interpersonal relationships). Limiting expectations to disease-related issues limits oppor-

tunities for adolescents to develop more appropriate and well-rounded identities as young people with a future, despite having a severe chronic illness. In general, adolescents with chronic illnesses face the same developmental tasks as adolescents without illness, and it is important not to label these adolescents as special or different in these tasks. Particular barriers (such as physical barriers for adolescents with mobility impairments or disincentives for employers to shoulder potentially higher health insurance premiums) may hinder the employment progress of young adults with chronic illnesses, but the basic task of increasing independence remains the same.

The prevalence data presented by Newacheck et al must be interpreted carefully. The authors knowingly chose a very broad definition of a chronic health condition: one that was present in the previous 12 months and first noted at least 3 months prior to the interview, except for certain conditions that are considered chronic, regardless of their duration prior to the time of interview (such as asthma, heart disease, or leukemia). Thus, an adolescent with a swimmer's ear in the year before the interview and a middle ear infection at some time during early childhood might be considered to have a chronic illness.

Furthermore, parental reports may be inaccurate, especially in re-

gard to such conditions as respiratory allergies, asthma, or heart diseases. For this last category, the estimates seem high, and one wonders whether parental interpretations of heart murmurs affected the response rates. Other condition-specific rates are surprising. Most studies of recurrent middle ear disease, for example, indicate a significantly higher prevalence among boys than girls, and the rates for anemia are higher than recent estimates from the Centers for Disease Control.

As the authors clearly explain, the rates reported here likely represent the upper limits of prevalence. It would have been interesting had the authors compared rates using broader and narrower definitions of chronic illness, yet the use of this data set requires certain difficult decisions, and Newacheck and colleagues chose wisely. Even if the high rates reported here are twice those of reality, their estimates still document a sizeable burden of chronic illness in this age group and the need for efforts to diminish the long-term consequences of chronic illness.

This study suggests two important further lines of research. First, what are the implications of physical limitations and behavioral consequences for the transition of adolescents with chronic illnesses to adulthood?⁴ How does this population compare with its counterparts without illness with respect to educational attainment, entering the job market, development of permanent relationships and families, and dependence on public institutions? Do adolescents with physical limitations or behavior problems face greater burdens or

barriers than those without such limitations? Does identification and treatment of these behavioral problems improve these outcomes?

The second important line of research is to explore the mechanisms by which chronic illness appears to place adolescents at higher risk of behavior problems. The current study does not report differences by condition groups with respect to the increased risk of behavior problems, but other studies⁵ suggest that the increased behavioral risks relate not to the specific health condition but rather to the fact of having a chronic illness, regardless of the specific diagnosis. Severity of illness also does not predict well the risk of behavior problems.⁶ In the current study, an increasing number of conditions was associated with a greater risk of behavior problems, suggesting that adolescents with more severe conditions may face higher risks. Yet, severity is very difficult to measure, especially across illnesses.⁷

Further, although the increased risk of behavior problems is clearly significant, both statistically and clinically, data presented by Newacheck and colleagues support the notion that most adolescents with chronic illnesses are psychologically healthy. What factors aid those adolescents to do well despite the burdens and tasks created by their chronic illness? How do self-esteem, parental factors, family structure, education, and social and health programs help to encourage this resilience? A clearer understanding of the roles of these many factors in influencing resilience and risk will help direct pediatric clinical attention to the most promising areas of prevention and intervention in the future.

Given the data presented by Newacheck et al, the need to assess physical and behavioral functioning in the context of developmentally appropriate pediatric care for adolescents with chronic illnesses seems increasingly clear. Helping to insure that chronic illness interferes as little as possible with the normal tasks and transitions of adolescence is a particularly important pediatric responsibility.

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The Evolution of Surgical Treatment for Congenital Cardiac Disease

The goals of reparative surgical therapy for any disease are to restore function and life expectancy to normal. The development of cardiopulmonary bypass and the implementation of techniques of reparative surgery for patients with

congenital cardiovascular malformations in the 1950s and 1960s introduced the reality of reparative surgery in patients with otherwise fatal cardiovascular disease. Attention was initially focused on ensuring survival through the surgical proce-

dures and in the early postoperative period. As the number of patients with "repaired" congenital cardiovascular disease increased, long-term follow-up of these patients became possible. The report by Morris and Menashe¹ in the *Journal of the*

American Medical Association analyzes long-term survival and the cause of late death after repair of eight common congenital cardiovascular malformations. This cohort of patients included all children from the state of Oregon who underwent reparative surgery for one of these congenital cardiac defects before age 18 years. The authors conclude that surgical repair of many congenital cardiovascular malformations is associated with lingering cardiac mortality and morbidity, particularly in patients with aortic stenosis, coarctation of the aorta, and transposition of the great arteries.

This report is notable for chronicling the evolution of the surgical treatment for congenital cardiac disease since the late 1950s. To that end, the authors note that the age at surgery and hospital mortality generally has diminished substantially during the last 30 years of cardiac surgery in Oregon. The causes of late mortality were described by these authors as primarily due to disturbances of cardiac rhythm, progressive ventricular dysfunction, and fixed pulmonary vascular obstructive disease resulting in pulmonary hypertension. As a report of long-term survival after reparative surgery for several common congenital cardiovascular malformations, this article is excellent and deserves further study.

This report leaves several unanswered questions that are central to the understanding of optimal treatment of patients with congenital heart disease. First, it could be expected that a group of patients with unusual or particularly severe malformations was excluded from surgical therapy or underwent only palliative surgery. To fully define the altered natural history of a congenital cardiovascular malformation, all patients with this diagnosis should be included in any evaluation, irrespective of surgical intervention. Second, one of the major strengths of this article is that the significant majority of patients were operated on at one institution, primarily under the leadership of one surgeon. This also proves to be a drawback in the interpretation of the information presented, since any single surgical group may have a greater or lesser degree of expertise in the surgical repair of certain malformations. Fi-

nally, the statistical analysis of the various groups of patients undergoing surgical therapy, as well as their late follow-up, may be made more robust with more sophisticated statistical analytic techniques (eg, hazard functions for death).

Many factors have contributed to improved survival after surgical repair of congenital cardiac disease. Perhaps foremost among them is our increased understanding of fetal and neonatal physiologic characteristics. This has led to an increased understanding of the natural history of many cardiovascular malformations, and has stimulated the development of medications specifically designed to alter natural postnatal physiologic changes (ie, prostaglandins to maintain patency of the ductus arteriosus). Our more profound understanding of neonatal physiologic features has permitted the development of techniques of intraoperative (ie, anesthetic) and postoperative treatment specifically designed for patients with congenital cardiac disease. Our complete understanding of anatomy has led to innovative surgical techniques and instrumentation that permit reparative surgery even in the very young. In many centers, reparative surgery is currently being offered early in life in patients with even the most complex congenital cardiovascular malformations.

There are numerous examples of the changes in surgical practice these advances have permitted. In spite of a calculated 20-year survival of 80% for an atrial inversion operation in certain hands, anatomical repair of transposition of the great arteries (arterial switch procedure) has become increasingly popular due to the well-documented incidence of atrial arrhythmias as well as progressive right ventricular dysfunction with atrial inversion procedures.² Furthermore, fewer palliative procedures are being performed on patients with tetralogy of Fallot, and earlier reparative surgery is being offered in most centers. This may have a favorable impact on long-term survival because of preservation of ventricular function.³ In patients with coarctation of the aorta, the single most important determinant of survival and freedom from persistent hypertension after repair is the age at opera-

tion. With increasing experience in relatively newer surgical techniques (eg, extended end-to-end anastomosis), it is quite possible that the incidence of restenosis and persistent hypertension after repair may be minimized in the long term. Of particular note in this subgroup of patients is the fact that the most common cause of death in patients undergoing repair of coarctation is progressive coronary artery disease.

An important issue raised by the authors of the current report¹ is the somewhat disquieting incidence of pulmonary hypertension, congestive heart failure, and ventricular arrhythmias leading to late death. A significant fraction of these patients may have had residual anatomic lesions, best treated with reoperation, or may have undergone surgical repair after irreversible physiologic changes occurred. Therefore, the findings of this historical review regarding postoperative morbidity and mortality may not be applicable and appropriate for patients undergoing corrective surgery today. Fundamental to the improved treatment of patients with congenital cardiovascular disease are the precepts of early detection, early reparative surgery, thoughtful and appropriate postoperative treatment, and meticulous long-term follow-up. It is only with a combination of all of these factors that long-term patient function and survival can be maximized.

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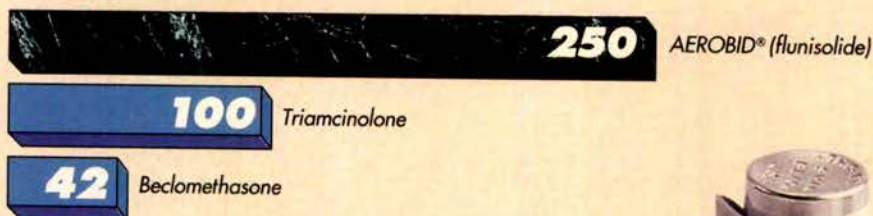
For Effective Control of Airway Inflammation

- **More mcg per puff**

AEROBID delivers 2.5 to 5 times as many mcgs per puff than those of the leading competitors.

AEROBID[®] vs competitive inhalers

Total mcg of inhaled steroid/puff²



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The only inhaled steroid that provides 2000 mcg per day.

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Please see accompanying brief summary which follows.

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AeroBid® (flunisolide)

Effective asthma control BID

For oral inhalation only

CONTRAINDICATIONS

AeroBid Inhaler is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

Particular care is needed in patients who are transferred from systemically active corticosteroids to AeroBid Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although AeroBid Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal if it falls at or near the normal mean level.

Localized infections with *Candida albicans* or *Aspergillus niger* have occurred in the mouth and pharynx and occasionally in the larynx. Positive cultures for oral *Candida* may be present in up to 34% of patients. Although the frequency of clinically apparent infection is considerably lower, these infections may require treatment with appropriate antifungal therapy or discontinuance with AeroBid Inhaler.

AeroBid Inhaler is not to be regarded as a bronchodilator and is not indicated for rapid relief of bronchospasm.

Patients should be instructed to contact their physician immediately when episodes of asthma that are not responsive to bronchodilators occur during the course of treatment. During such episodes, patients may require therapy with systemic corticosteroids.

There is no evidence that control of asthma can be achieved by administration of the drug in amounts greater than the recommended doses, which appear to be the therapeutic equivalent of approximately 10 mg/day of oral prednisone. Theoretically, the use of inhaled corticosteroids with alternate day prednisone systemic treatment should be accompanied by more HPA suppression than a therapeutically equivalent regimen of either alone.

Transfer of patients from systemic steroid therapy to AeroBid Inhaler may unmask allergic conditions previously suppressed by the systemic steroid therapy, e.g., rhinitis, conjunctivitis, and eczema.

PRECAUTIONS

General: Because of the relatively high molar dose of flunisolide per activation in this preparation, and because of the evidence suggesting higher levels of systemic absorption with flunisolide than with other comparable inhaled corticosteroids, patients treated with AeroBid should be observed carefully for any evidence of systemic corticosteroid effect, including suppression of bone growth in children. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of a decrease in adrenal function. During withdrawal from oral steroids, some patients may experience symptoms of systemically active steroid withdrawal, e.g., joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement of respiratory function.

In responsive patients, flunisolide may permit control of asthmatic symptoms without suppression of HPA function. Since flunisolide is absorbed into the circulation and can be systemically active, the beneficial effects of AeroBid Inhaler in minimizing or preventing HPA dysfunction may be expected only when recommended dosages are not exceeded.

The long-term effects of the drug in human subjects are still unknown. In particular, the local effects of the agent on developmental or immunologic processes in the mouth, pharynx, trachea, and lung are unknown. There is also no information about the possible long-term systemic effects of the agent.

The potential effects of the drug on acute, recurrent, or chronic pulmonary infections, including active or quiescent tuberculosis, are not known. Similarly, the potential effects of long-term administration of the drug on lung or other tissues are unknown.

Pulmonary infiltrates with eosinophilia may occur in patients on AeroBid Inhaler therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhalational steroids are administered, a causative role for the drug and/or its vehicle cannot be ruled out.

Carcinogenesis: A 22-month study was conducted in Swiss derived mice to evaluate the carcinogenic potential of the drug. There was an increase in the incidence of pulmonary adenomas within the range of adenomas previously reported in the literature for untreated or control Swiss derived mice. An additional study is being conducted in a species with a lower incidence of spontaneous pulmonary tumors.

Impairment of fertility: Female rats receiving high doses of flunisolide (200 mcg/kg/day) showed some evidence of impaired fertility. Reproductive performance in the low (8 mcg/kg/day) and mid-dose (40 mcg/kg/day) groups was comparable to controls.

Pregnancy: Pregnancy Category C. As with other corticosteroids, flunisolide has been shown to be teratogenic in rabbits and rats at doses of 40 and 200 mcg/kg/day respectively. It was also fetotoxic in these animal reproductive studies. There are no adequate and well-controlled studies in pregnant women. Flunisolide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when flunisolide is administered to nursing women.

ADVERSE REACTIONS

Adverse events reported in controlled clinical trials and long-term open studies in 514 patients treated with AeroBid are described below. Of those patients, 463 were treated for 3 months or longer, 407 for 6 months or longer, 287 for 1 year or longer, and 122 for 2 years or longer.

Musculoskeletal reactions were reported in 35% of steroid-dependent patients in whom the dose of oral steroid was being tapered. This is a well-known effect of steroid withdrawal.

Incidence 10% or greater

Gastrointestinal: diarrhea (10%), nausea and/or vomiting (25%), upset stomach (10%); **General:** flu (10%); **Mouth and Throat:** sore throat (20%); **Nervous System:** headache (25%); **Respiratory:** cold symptoms (15%), nasal congestion (15%), upper respiratory infection (25%); **Special Senses:** unpleasant taste (10%).

Incidence 3-9%

Cardiovascular: palpitations; **Gastrointestinal:** abdominal pain, heartburn; **General:** chest pain, decreased appetite, edema, fever; **Mouth and Throat:** candida infection; **Nervous System:** dizziness, irritability, nervousness, shakiness; **Reproductive:** menstrual disturbances; **Respiratory:** chest congestion, cough, hoarseness, rhinitis, runny nose, sinus congestion, sinus drainage, sinus infection, sinusitis, sneezing, sputum, wheezing; **Skin:** eczema, itching (pruritus), rash; **Special Senses:** ear infection, loss of smell or taste.

Incidence 1-3%

General: chills, increased appetite and weight gain, malaise, peripheral edema, sweating, weakness; **Cardiovascular:** hypertension, tachycardia; **Gastrointestinal:** constipation, dyspepsia, gas; **Hemic/Lymph:** capillary fragility, enlarged lymph nodes; **Mouth and Throat:** dry throat, glossitis, mouth irritation, pharyngitis, phlegm, throat irritation; **Nervous System:** anxiety, depression, faintness, fatigue, hyperactivity, hypoactivity, insomnia, moodiness, numbness, vertigo; **Respiratory:** bronchitis, chest tightness, dyspnea, epistaxis, head stuffiness, laryngitis, nasal irritation, pleurisy, pneumonia, sinus discomfort; **Skin:** acne, hives, or urticaria; **Special Senses:** blurred vision, earache, eye discomfort, eye infection.

Incidences less than 1%, judged by investigators as possibly or probably drug-related: abdominal fullness, shortness of breath.

*The incidences as shown of cough, wheezing, and chest tightness were judged by investigators to be possibly or probably drug-related. In placebo-controlled trials, the overall incidences of these adverse events (regardless of investigators' judgement of drug relationship) were similar for drug and placebo-treated groups. They may be related to the vehicle or delivery system.

CAUTION: Federal law prohibits dispensing without prescription. For full prescribing information, please see package insert.

(NDC 0456-0672-99)

Mfd by: Riker Laboratories
Northridge, California 91324

For: Forest Pharmaceuticals, Inc.
St. Louis, MO 63043-9979

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Prevalence and Impact of Chronic Illness Among Adolescents

Paul W. Newacheck, DrPH; Margaret A. McManus, MHS; Harriette B. Fox, MSS

• A sample of 7465 persons aged 10 to 17 years from the 1988 National Health Interview Survey on Child Health was used to assess the prevalence and impact of chronic conditions in adolescents. We defined a condition as chronic if it was first noted more than 3 months before the interview or a condition that ordinarily would be of lengthy duration, such as arthritis or heart disease. An estimated 31.5% of US adolescents were reported to have one or more chronic conditions. The most commonly reported chronic conditions included respiratory allergies, asthma, and frequent or severe headaches. Chronic conditions had widely varying impact on adolescent activity levels. On average, adolescents with chronic conditions experienced 3.4 bed days and 4.4 school absence days related to their chronic conditions in the year before the interview. Adolescents with chronic conditions were also reported to experience 35% more behavioral problems than their counterparts without chronic conditions. Adolescents with multiple chronic conditions had substantially more bed days, school absence days, and behavioral problems than adolescents with a single chronic condition. Implications of these findings are discussed. (AJDC. 1991;145:1367-1373)

Adolescence is a period of major transition in physical, psychologic, and social development. Normal adolescent development can be extremely variable in terms of height, weight, sexual maturation, identity formation (eg, increasing independence from family), intellectual ability, and psychologic development. Health status also varies among adolescents, but most appear quite healthy when traditional health status measures are used. For example, most adolescents are reported to be in excellent or very good health; they suffer from fewer acute illnesses than their younger counterparts, and their mortality rates are low compared with those of adults. However, a significant portion of this population suffers from developmental and transitional stresses, adverse consequences of

risk-taking behaviors, and other morbidities, including chronic illness.¹⁻⁵

Chronic physical and mental illnesses are an important contributor to adolescent morbidity. National survey data indicate that approximately 6% of US adolescents suffer from chronic illnesses that result in some limitation of activity or disability.⁶ There is also evidence to suggest that the burden of chronic illness has been growing for adolescents. Specifically, advances in diagnosis and treatment have dramatically changed mortality rates for both children and adolescents with chronic conditions, with the result being that many adolescents with life-threatening chronic conditions now survive into adulthood.

For example, in 1940, the median length of survival for children with cystic fibrosis was 2 years; in 1970, it rose to 15 years, and in 1990 the mean life expectancy was 28 years (S.C. Fitzsimmons, PhD, unpublished data, 1991, Cystic Fibrosis Patient Registry, Cystic Fibrosis Foundation, Bethesda, Md). While not as dramatic, sizable improvements in longevity have also been demonstrated for certain forms of leukemia and heart conditions.⁷ There is also evidence, although it is somewhat controversial, of an increase in the prevalence of severe, but generally not life-threatening conditions, such as asthma, orthopedic impairments, and visual and hearing problems among children and adolescents.⁸

For those with no significant health problems, the biologic, psychologic and social transitions that accompany adolescence are stressful, but for the less fortunate adolescent with a chronic illness this period of transition can impose added burdens, ranging from excessive dependence on families to low self-esteem. Previous studies have demonstrated a clear association between presence of chronic physical conditions and behavioral problems among adolescents.⁹ Indeed, the increasing burden of chronic physical illnesses referenced above may be both a cause and a consequence of psychologic and behavioral problems among adolescents.

Despite renewed concern over the plight of chronically ill adolescents, relatively little is known about the prevalence of chronic conditions or their impact. Previous studies have combined children and adolescents, focused on subgroups of the adolescent population (eg, younger adolescents or disabled adolescents), or relied on clinic populations or localized samples that may not be gener-

Accepted for publication May 20, 1991.

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alizable. No recent studies provide a profile of adolescent chronic conditions.

Release of the 1988 National Health Interview Survey (NHIS) on Child Health permits a new and current assessment of the prevalence and impact of chronic conditions among adolescents. We used this nationally representative data set to provide estimates of the prevalence of a variety of chronic conditions among adolescents aged 10 to 17 years; describe the impact of chronic conditions, especially multiple chronic conditions, on adolescent activity levels; and investigate the relationship between chronic conditions and behavioral problems among adolescents.

SUBJECTS AND METHODS

The NHIS is a continuing nationwide household survey conducted by the US Bureau of the Census for the National Center for Health Statistics.¹⁰ The sample is designed to be representative of the civilian noninstitutional population. Each year interviews are conducted in approximately 45 000 households, including about 135 000 persons. This makes the NHIS the largest general-purpose health survey conducted in the United States.

In 1988, a special supplemental questionnaire on child and adolescent health was included in the survey. This supplemental questionnaire is similar to one that was fielded for the first time in 1981. The 1988 questionnaire, like its predecessor, covered a range of topics relevant to child health, including child care, pregnancy and birth, sleep habits, behavioral problems, developmental problems, other health problems, and use of health services. This questionnaire was administered for one randomly selected child or adolescent in each household. Interviews were completed for 91% of all eligible children and adolescents, resulting in a sample of 17 110 persons ranging in age from newborn to 17 years.¹¹ We used the entire sample of 7465 adolescents aged 10 to 17 years for this analysis.

Of particular importance for our purposes was the inclusion of a detailed checklist of childhood health problems in the supplement. Respondents were read this extensive list of conditions and asked whether the sample adolescent had any of these conditions during the previous 12 months. In this manner, prevalence estimates could be derived for more than 50 distinct adolescent health conditions, including such diverse conditions as urinary tract infections, asthma, and cerebral palsy, but excluding minor acute illnesses, such as colds, influenza, and minor injuries. The conditions included in the checklist were primarily those of a physical nature. Mental health conditions were largely excluded from the checklist due to past underreporting of such conditions in household interviews.

The large sample combined with this lengthy checklist provided an opportunity to examine adolescent health problems in a more comprehensive fashion than was possible from past national surveys. In particular, data on the impact of checklist conditions were collected for the first time. These data permit analyses of the impact of chronic conditions on adolescent activity levels and analyses of hospital and ambulatory care use for different types of childhood chronic conditions.

We asked a panel of eight pediatricians to review the checklist conditions to determine whether any should be excluded from our analysis of chronic conditions. Where a majority of the pediatricians considered a checklist condition not to be chronic, it was eliminated. Eight conditions were eliminated in this fashion, including pneumonia, repeated tonsillitis, mononucleosis, meningitis, urinary tract infection, seizures with fever, enuresis, and conditions requiring surgery but not otherwise specified. We then classified the remaining conditions according to chronicity using conventions similar to those developed by the Division of Health Interview Statistics of the National Center for Health Statistics.¹⁰

Specifically, a condition was considered chronic if the respondent indicated it was first noticed more than 3 months before the interview or it was a type of condition that ordinarily has a du-

ration of more than 3 months. Examples of conditions that are considered chronic regardless of their time of onset include diabetes, heart conditions, and arthritis. Because no severity criteria were used, this approach to defining chronic illness leads to inclusion of a large number of conditions. Still, we think the definition is useful, particularly for providing an upper-bound estimate of the size of the chronically ill child population.

To enable a manageable analysis and presentation, conditions were grouped into 19 broader categories, including five impairment groupings and 14 disease groupings. The categorization scheme is based on grouping conditions that are clinically related while taking into account sample size limitations. The disease categorization includes conditions with active disease. Impairments are chronic or permanent defects, usually static in nature, that result from disease, injury, or congenital malformation. The overall categorization scheme and condition groupings are illustrated in Table 1.

In addition to the checklist of child health conditions, NHIS respondents were also asked an extensive series of structured questions concerning adolescent behavioral problems. The 26 questions dealt with specific problem behaviors present during the year before the interview and were derived from the Achenbach Behavior Problems checklist and other child behavior scales.¹²⁻¹⁴ Using the checklist results, we scored adolescents according to a behavioral problems index with five subscales originally developed by Zill.¹⁵

The subscales include from four to six items and represent some of the more common syndromes of problem behaviors among adolescents. The five subscales include the following: (1) antisocial behavior; (2) anxiety and depressed mood; (3) hyperactive behavior; (4) headstrong behavior; and (5) peer conflict and social withdrawal. Using data from the predecessor 1981 survey, the internal consistency reliability of the overall index was found to be α equals .91 for adolescents. The α coefficients for the subscales ranged from .70 to .76.¹⁵

Since the behavioral problem subscales contain a variable number of items, the results presented here have been converted into index or ratio scores. In addition, because different sets of questions were used for sample persons younger than 12 years and those aged 12 years and older, we restricted our analysis to the population aged 12 years and older.

In reviewing the NHIS results presented here, one should keep in mind that the results are based on household interviews, not clinical tests or medical examinations. In the case of adolescents, an adult member of the household knowledgeable about the adolescent's health, usually the mother, served as the respondent. Thus, the NHIS results represent the mother's or other adult's perception of the adolescent's health. Although great effort was made to ensure accurate reporting, the information obtained might be inaccurate because the respondent might have been unaware of relevant information, have forgotten it, or have been unwilling to report certain types of information. For example, parents might be unwilling to report certain potentially "embarrassing" or stigmatic conditions, such as behavioral problems.

The results of our analysis are presented in simple tabular form. The observations were weighted according to the inverse of their sampling probabilities so that the estimates presented reflect national population totals. Standard errors were calculated using software that accounts for the complex sample design of the NHIS.^{16,17} Relative SEs were obtained by dividing the SE of the estimate by the estimate itself. Readers should interpret estimates with large SEs with caution. This especially applies to estimates for conditions of comparatively low prevalence, such as cerebral palsy, juvenile diabetes, and sickle cell disease.

RESULTS Prevalence

Of an estimated 27.2 million adolescents aged 10 to 17 years in the United States, 31.5%, or 8.6 million, had one or more chronic conditions in 1988, according to the NHIS (Table 2). The majority of adolescents with chronic condi-

Table 1.—Chronic Conditions

Condition Category	Checklist Conditions
Impairments	
Musculoskeletal	Missing limbs, fingers, or toes*; permanent impairment*; stiffness or deformity of back or side, limbs, fingers, or toes*
Deafness and hearing loss	Deafness or trouble hearing in one ear*; deafness or trouble hearing in both ears*
Blindness and visual impairment	Blindness in one eye*; blindness in both eyes*; crossed eyes*; any other trouble seeing*
Speech defects	Stammering or stuttering; any other speech defect
Cerebral palsy	Cerebral palsy*
Disease	
Diabetes	Diabetes*
Sickle cell disease	Sickle cell anemia*
Anemia	Anemia
Asthma	Asthma*
Eczema and skin allergies	Eczema or any other skin allergy*
Epilepsy and seizures	Epilepsy or convulsions without fever*
Arthritis	Arthritis or other joint problem*
Heart disease	Congenital heart disease*; any other heart disease or condition*
Frequent ear infections	Frequent or repeated ear infections
Frequent diarrhea/bowel trouble	Frequent or repeated diarrhea or colitis; any other persistent bowel trouble
Digestive allergies	Any food or digestive allergy
Frequent or severe headaches	Frequent or severe headaches, including migraines
Other	Mononucleosis; hepatitis; meningitis; rheumatic fever*; seizures associated with fever; other bone, cartilage, muscle, or tendon problem; conditions requiring surgery; conditions lasting more than 3 months

*Condition deemed chronic regardless of date of onset; other conditions deemed chronic if first noted more than 3 months before the interview.

Table 2.—Prevalence of Chronic Conditions Among US Adolescents

No. of Chronic Conditions	n	No. per 100 Adolescents	SE	Population Estimate
0	5098	68.5	0.7	18 621 000
1	1585	21.3	0.5	5 776 000
2	539	7.0	0.4	1 910 000
≥3	243	3.2	0.3	875 000

Table 3.—Prevalence of Chronic Conditions Among US Adolescents According to Sociodemographic Characteristics

Characteristic	Prevalence of Chronic Conditions per 100 Adolescents	SE	Population Estimate
Age, y			
All ages	31.5	0.7	8 561 000
10 to 13	31.0	0.9	4 138 000
14 to 17	31.9	0.9	4 423 000
Sex			
M	32.1	1.0	4 453 000
F	30.9	0.9	4 108 000
Race and ethnicity			
White	34.8	0.8	6 576 000
Black	23.7	1.5	981 000
Hispanic	24.0	2.4	723 000
Other	25.5	2.9	282 000
Poverty status			
At or below poverty level	30.1	1.9	1 184 000
Above poverty level	32.4	0.8	7 026 000
Region			
Northeast	31.5	1.2	1 548 000
Midwest	33.0	1.2	2 353 000
South	28.0	1.4	2 673 000
West	35.5	1.5	1 988 000
Residence			
Central city	28.8	1.2	2 247 000
Suburbs	32.4	1.0	4 171 000
Nonmetropolitan	32.8	1.3	2 143 000

tions had only one such condition, but a significant minority were afflicted with multiple chronic conditions. Specifically, 7% of all adolescents were reported to have two chronic conditions and 3% had three or more conditions. Put another way, nearly one third of adolescents with chronic conditions had multiple conditions.

Prevalence of chronic conditions was surprisingly similar among adolescents with widely different sociodemographic characteristics (Table 3). The overall prevalence of

chronic conditions was almost identical between younger adolescents, aged 10 to 13 years, and older adolescents, aged 14 to 17 years, as well as between boys and girls. Table 3 reveals that there was also little difference in the overall prevalence of chronic conditions by poverty status. Some modest differences are apparent by region and residence. Specifically, chronic conditions were more prevalent in the West than in the South ($P<.01$) and among adolescents living in suburban and rural areas

Table 4.—Age and Sex Differences in Prevalence of Chronic Conditions

Condition	All Adolescents	Cases per 1000 US Adolescents			
		Age, y		Sex	
		10 to 13	14 to 17	M	F
All children with conditions	315.0	310.4	319.3	320.5	309.1
Impairment					
Musculoskeletal impairments	20.9	13.6	28.0	20.2	21.7
Deafness and hearing loss	17.0	18.9	15.2	20.6	13.3
Blindness and visual impairment	16.0	17.2	14.8	12.5	19.6
Speech defects	18.9	23.6	14.5	26.6	10.9
Cerebral palsy	1.2*	0.5*	1.8*	0.9*	1.4*
Disease					
Diabetes	1.5*	0.8*	2.2*	2.4*	0.6*
Sickle cell disease	0.9*	0.6*	1.2*	0.9*	1.0*
Anemia	5.8	4.6	6.9	3.0	8.6
Asthma	46.8	48.7	44.9	51.2	42.1
Respiratory allergies	130.3	127.6	132.8	139.9	120.2
Eczema and skin allergies	35.2	32.9	37.5	31.6	39.1
Epilepsy and seizures	3.3	2.7*	3.8*	2.1*	4.5*
Arthritis	8.7	5.3	11.9	8.1	9.3
Heart disease	17.4	14.8	19.8	19.0	15.7
Frequent or repeated ear infections	33.6	41.8	25.8	32.6	34.7
Frequent diarrhea/bowel trouble	9.6	8.6	10.6	10.1	9.0
Digestive allergies	21.1	26.7	15.8	22.2	20.0
Frequent or severe headaches	45.8	40.3	51.2	41.1	50.8
Other	30.0	21.2	38.5	27.3	32.8

*Relative SE exceeds 30% of estimate value.

compared with central city areas ($P < .05$). Larger differences are apparent by race and ethnicity. Specifically, chronic conditions were reported much more frequently for whites than for blacks ($P < .01$), Hispanics ($P < .01$), and other minority adolescents ($P < .01$).

Prevalence estimates for 19 categories of chronic conditions are shown in Table 4. Respiratory allergies (eg, hay fever) ranked as the leading chronic condition, affecting 13% of all adolescents. Asthma ranked second, affecting 5% of all adolescents. The third and fourth ranking conditions, headaches and skin conditions, were substantially less prevalent, each affecting fewer than 5% of US adolescents in 1988. The fifth leading condition affecting adolescents was recurrent ear infections.

Although little difference was apparent in the overall prevalence of chronic conditions among younger and older adolescents, substantial differences in the prevalence of individual conditions by age can be seen in Table 4. For example, speech defects and digestive allergies were almost twice as prevalent among younger adolescents ($P < .05$), while musculoskeletal impairments and arthritis were at least twice as prevalent among older adolescents ($P < .01$). Clearly, the illness burden is substantially different for younger and older adolescents even if the overall prevalence of chronic conditions is similar for the two age groups.

Like the pattern for age, the absence of an overall prevalence difference by gender masks a number of substantial condition-specific prevalence differentials (Table 4).

For example, boys were reported to be more than twice as likely as girls to have speech defects ($P < .01$). Girls were more than twice as likely as boys to be reported to have anemia ($P < .05$).

Impact on Activities

The impact of chronic conditions on adolescent activity levels is shown in Table 5. On average, adolescents with one or more chronic conditions spent 3.4 days ill in bed and missed 4.4 days from school in the year before the interview due to their chronic conditions. These restricted activity days are entirely attributable to chronic conditions and are in addition to those caused by acute illnesses. Hence, they reflect the added illness burden faced by children with chronic conditions. Nationally, a total of 29 million bed days and 38 million school absence days were attributable to adolescent chronic conditions in 1988. The largest number of bed days and school loss days were reported for adolescents afflicted with arthritis, asthma, and heart disease. However, it should be noted that the precision of bed day and school loss day estimates is limited for many of the conditions shown in Table 5.

The last column of Table 5 shows the percentage of adolescents reported to have experienced limitation of activity due to chronic conditions. Adolescents who are limited in their activities include those who are unable to attend school, those limited in the amount or kind of school activities they can engage in, and adolescents who are limited in extracurricular activities, such as sports or

Table 5.—Impact of Chronic Conditions on US Adolescents

Condition	Mean No. of Bed Days	Mean No. of School Absence Days	% of Adolescents With Limitation of Activity
All children with chronic conditions	3.4	4.4	15.7
Impairment			
Musculoskeletal impairments	1.3*	2.7*	35.5
Deafness and hearing loss†	29.5
Blindness and visual impairment†	21.5
Speech defects†	41.2
Cerebral palsy	3.7*	3.7*	100.0
Disease			
Diabetes	0.7*	0.4*	18.8*
Sickle cell disease	0.5*	0.4*	20.6*
Anemia	1.4*	1.4*	18.4*
Asthma	3.2	4.6	28.8
Respiratory allergies	0.7	1.3	12.1
Eczema and skin allergies†	12.9
Epilepsy and seizures	3.8*	3.7*	74.4
Arthritis	4.0*	3.5*	24.6
Heart disease	2.4*	1.6*	23.0
Frequent or repeated ear infections	1.5	2.3	15.7
Frequent diarrhea/bowel trouble	0.7*	1.4	32.2
Digestive allergies	0.4	1.0	21.9
Frequent or severe headaches	3.2	3.6	17.0
Other	3.5	4.0	22.8

*Relative SE exceeds 30% of estimate value.

†Information on bed days and school absences was not obtained for these conditions.

after-school work. Overall, 16% of adolescents with chronic conditions were reported to be limited in their activities. The percentage of adolescents with limitation of activity ranged from a low of 12% for adolescents with respiratory and skin allergies to a high of 100% for adolescents with cerebral palsy.

One might expect adolescents with more than one chronic condition to experience greater restriction of their activities compared with adolescents with only a single chronic condition. This is indeed the case, as is shown in Table 6. Adolescents with two chronic conditions had almost twice as many bed days and school absence days as adolescents with only one condition ($P<.05$). They were also more than twice as likely to be reported as being limited in their activities ($P<.01$). Adolescents with three or more chronic conditions had about twice as many days ill in bed ($P<.01$) and lost from school ($P<.05$) as adolescents with two chronic health problems. Similarly, they were much more likely than their counterparts with two conditions to be limited in their activities ($P<.05$). Hence, the detrimental impact of chronic conditions on adolescent activity levels increases substantially with the number of conditions reported.

Impact on Behavior

Adolescents with chronic conditions are more likely than their counterparts without chronic conditions to experience behavioral problems (Table 7). Based on the Behavioral Problems Index, adolescents aged 12 to 17 years with one or more chronic conditions had 35% more behavioral problems than adolescents with no chronic

conditions ($P<.01$). Chronically ill adolescents scored higher than adolescents without chronic conditions on each of the five subscales shown in Table 7 ($P<.01$), especially the subscale reflecting peer conflict and social withdrawal. This latter subscale included these four items: (1) trouble getting along with other children; (2) not being liked by other children; (3) being withdrawn; and (4) feeling that others are out to get him or her.

There is also a clear progressive relationship between the number of chronic conditions and the number of behavioral problems reported. Adolescents with one chronic condition were reported to have 23% more behavioral problems on average than adolescents with no chronic conditions ($P<.01$). Adolescents with two chronic conditions experienced 45% more behavioral problems than adolescents with no chronic conditions ($P<.01$), and those with three or more chronic conditions had 82% more behavioral problems than adolescents without chronic conditions ($P<.01$). Similar relationships were found for each of the subscales. Again, the most powerful association between chronic conditions and behavioral problems is apparent for the peer conflict and social withdrawal subscale. Adolescents with three or more chronic conditions scored more than twice as high on this subscale as adolescents with no chronic conditions ($P<.01$).

COMMENT

A substantial number of adolescents aged 10 to 17 years are affected by chronic conditions. According to the NHIS on Child Health, as many as 8.6 million or 31.5% of adolescents had one or more chronic conditions in 1988. This

Table 6.—Impact of Multiple Chronic Conditions on US Adolescents

No. of Chronic Conditions	Mean No. of Bed Days	Mean No. of School Absence Days	% of Adolescents With Limitation of Activity
1	2.5	3.0	9.9
2	3.9	5.8	24.4
≥3	8.0	8.9	35.1

Table 7.—Association Between Chronic Conditions and Behavioral Problems Among US Adolescents

No. of Chronic Conditions	Behavioral Problem Index Ratios					
	Total	Anxiety and Depressed Mood	Headstrong	Antisocial	Hyperactive	Peer Conflict and Social Withdrawal
0	1.00	1.00	1.00	1.00	1.00	1.00
≥1	1.35	1.40	1.29	1.21	1.31	1.64
1	1.23	1.29	1.21	1.13	1.21	1.39
2	1.45	1.51	1.36	1.20	1.46	1.86
≥3	1.82	1.79	1.59	1.73	1.67	2.57

estimate is quite similar to the 30.8% prevalence estimate derived for children younger than age 10 years using the same survey data set and definition of chronic illness.¹⁸

Surprisingly few differences were found in the overall prevalence of chronic conditions among adolescents by age, gender, and poverty status. In contrast, the survey results revealed significant variation in prevalence of chronic conditions by race and ethnicity. Further assessment is needed to determine if these results are attributable to reporting or interviewer biases, since they differ from previous studies of adolescents with severe chronic conditions. For example, one previous study of adolescents with activity-limiting chronic conditions showed no difference in prevalence for whites and minorities.⁶

The National Center for Health Statistics has conducted no studies of how reliably childhood chronic conditions are reported in NHIS interviews. However, previous comparisons of NHIS interview results with medical records among adults indicate that chronic conditions with some impact on a person's activities and conditions associated with recent medical encounters are generally accurately reported in household interviews, but conditions with little functional impact are frequently underreported when compared with physician records. The most recent study of NHIS interviewing methods found that between 35% and 45% of conditions were underreported, while between 8% and 12% of conditions were overreported compared with medical records. Those conditions most likely to be underreported include conditions related to the urinary and reproductive systems, mental illness, and cancer.^{19,20}

The prevalence estimates presented in this article do not take severity into account. Consequently, not all of the conditions categorized as chronic are likely to be of clinical or personal significance. Indeed, most of these conditions had apparently quite mild impact on adolescent activity levels. For example, 84% of adolescents with chronic conditions had no long-term limitations in their activities as a result of their chronic conditions.

While modest overall, the impact of chronic illness, as measured by days spent in bed, school absence days, and

limitation of activity, varied by specific impairment or disease. Respiratory allergies, the most common chronic conditions among adolescents, tended to have relatively minor impact on children's activities, while cerebral palsy, one of the least common conditions, tended to have quite severe impact on adolescents. Adolescents with respiratory allergies had below-average rates of bed days, school absences, and limitation of activity. They were reported to have less than 1 bed day per year and fewer than one in eight adolescents were reported to be limited in their activities. Adolescents with cerebral palsy were reported to have above-average rates of bed days, and the entire sample was reported to experience some limitation of activity.

Although not shown in the Tables, we also found tremendous variation in bed days and school absence days among adolescents with the same condition. Similar results have been found in other studies of childhood chronic conditions, leading some researchers to conclude that there may be as much variation in severity within disease categories as between disease categories.²¹ These results indicate that there is a need to identify new ways of accurately measuring the impact of chronic illness besides simply identifying the presence or absence of a chronic condition or the type of chronic condition.

In addition to their impact on physical activities, chronic conditions were associated with a variety of behavioral problems, including anxiety, depression, hyperactivity, peer conflict, and social withdrawal, as well as behaviors reflecting antisocial tendencies. Although all of those types of problem behaviors were more common among adolescents with chronic conditions than adolescents without chronic conditions, the analysis revealed that behavioral problems related to peer conflict and social withdrawal were especially pronounced among adolescents with chronic illness. These findings are similar to those reported in an earlier study of the relationship between chronic physical conditions and behavioral problems using the 1981 NHIS on Child Health and underscore the importance of increased attention on the part of

pediatricians and other child health professionals to the behavioral problems of chronically ill adolescents.⁹

Up until now little has been known about the impact of multiple chronic conditions on adolescents. Results from this study indicate that about 10% of US adolescents suffer from multiple chronic conditions. The impact of multiple conditions on adolescents, measured in terms of restricted activity days, limitation of activity, and behavioral problems, is substantially greater than the impact experienced by adolescents with a single chronic condition. For instance, adolescents with three or more conditions spent more than twice as many days in bed and out of school and were more than three times as likely to suffer from limitation of activity as those adolescents with only one chronic condition. In addition, adolescents with multiple chronic conditions were significantly more apt to experience behavioral problems, especially those related to peer conflict and social withdrawal.

Pediatric health care providers serving adolescents need to be especially sensitive to the greater needs of adolescents with multiple chronic conditions. The results of this analysis clearly underscore the need to focus additional attention on adolescents with multiple conditions. Further efforts by child health professionals are needed to address early intervention, to promote coordinated service provision systems that integrate health and mental health services, and to develop improved private and public benefit plans that take into account the greater intensity of health services required by adolescents with multiple conditions.

It is important, too, for other professionals serving adolescents to be familiar with the special situation of those with chronic conditions, particularly those with multiple chronic conditions. Teachers, guidance counselors, mental health professionals, and others need to understand that the normal social and developmental challenges of adolescence are especially difficult for this population. Achieving separation from parents, establishing satisfying peer group relationships, and planning for college or work are among the tasks that may require sustained and coordinated input from various professionals.

Ideally, adolescents with multiple or severe chronic conditions would be served by multidisciplinary teams able to support them through transitional periods. Achieving this goal, however, requires that greater attention be devoted to adolescents with special needs in basic and continuing education programs for professionals who serve them. It also requires that the salary and reimbursement structures for compensating these professionals be altered to provide financial incentives for collaborative and consultative activities.

This study was supported in part by grants MCH-067031-01 and MCH-067026-01 from the Maternal and Child Health Bureau. Additional support was provided by the National Institute for Disability and Rehabilitation Research through the Center for Children With Chronic Illness and Disability. Data were provided by the National Center for Health Statistics. The authors appreciate the helpful suggestions of the Research Consortium on Chronic Illness in Childhood and thank Helen Gonzales for preparing the manuscript.

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The Role of Corticosteroid Therapy in Children With Pneumococcal Meningitis

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• The records of 97 infants and children with pneumococcal meningitis treated in Dallas, Tex, from 1984 to 1990 were reviewed to determine whether corticosteroid therapy improved disease outcome as has been demonstrated in patients with *Haemophilus* meningitis. Forty-one patients received corticosteroid therapy, 39 of whom were given dexamethasone in the conventional 4-day regimen. There were no significant differences in the demographic and clinical characteristics of steroid- and non-steroid-treated patients. In addition, there were no significant differences between treatment groups with regard to presence of seizures, subdural effusions, hydrocephalus, and positive cerebrospinal fluid cultures 24 hours after the start of treatment. When steroid therapy was given before or concurrently with antibiotic therapy, none of 30 steroid-treated vs 16 of 52 non-steroid-treated patients developed evidence of neurologic or cardiovascular instability after the first parenteral antibiotic dose was given. Among 86 survivors examined, significantly fewer steroid-treated patients had an adverse neurologic long-term outcome, including hearing impairment, compared with non-steroid-treated patients (four of 35 vs 14 of 43). This was also true for those patients with overwhelming meningeal infection. We believe that corticosteroid therapy is also beneficial in infants and children with pneumococcal meningitis.

(AJDC. 1991;145:1374-1378)

The incidence of pneumococcal meningitis in the United States is approximately 1.1 cases per 100 000 population. It is more common in children, with a peak incidence of 30 cases per 100 000 in infants 3 to 5 months of age.¹ In our institution, *Streptococcus pneumoniae* accounted for 10% of the 2766 cases of bacterial meningitis in infants and children treated from 1969 through 1990. *Haemophilus influenzae* was the most common meningeal pathogen. The 10% case-fatality and 20% to 30% morbidity rates in children with pneumococcal meningitis have changed very little in the past 30 years despite the avail-

ability of more potent antibiotics that have high cerebrospinal fluid (CSF) bactericidal activity.^{1,2}

In experimental pneumococcal meningitis, bacterial lysis resulting from antibiotic therapy causes release into CSF of cell wall fragments that are responsible for local induction of proinflammatory cytokines, including interleukin 1 and tumor necrosis factor.^{3,4} These and other inflammatory proteins promote a destructive leukocyte-cerebral capillary endothelial cell interaction, platelet-mediated thrombosis, and cytotoxic, interstitial, and vasogenic cerebral edema.^{5,6} These events cause increased blood-brain barrier permeability to leukocytes and to low-molecular-weight serum proteins and can alter cerebral blood flow. In the rabbit pneumococcal meningitis model, anticytokine antibodies reduced CSF leukocytosis and brain edema,⁶ whereas monoclonal antibodies to CD11/CD18 leukocyte receptors involved in endothelial adhesion markedly reduced recruitment of leukocytes into the CSF, brain edema, and mortality in treated animals compared with untreated animals.⁷ As in the experimental *H influenzae* meningitis model,^{8,9} dexamethasone therapy markedly reduced the meningeal leukocyte mass,¹⁰ brain edema, CSF pressure, and lactate concentrations¹¹ in experimental pneumococcal meningitis.

Because of the similarities in the molecular pathophysiologic activity and modulatory effects of dexamethasone therapy in these two experimental meningitis models, it seemed reasonable to assume that dexamethasone therapy might be effective in infants and children with pneumococcal meningitis, as it has been demonstrated in Dallas and Costa Rican children with meningitis caused predominantly by *H influenzae*.^{12,13} We reviewed our experience with 97 infants and children with pneumococcal meningitis, 41 of whom received corticosteroid therapy.

PATIENTS AND METHODS

The records of all patients admitted to either Parkland Memorial Hospital or Children's Medical Center, Dallas, Tex, with pneumococcal meningitis from January 1984 through September 1990 were reviewed. Of the 98 patients admitted, 27 were enrolled in one of three double-blind, placebo-controlled trials of dexamethasone therapy; 23 were enrolled in prospective evaluations of antimicrobial agents; and the remaining 47 patients either declined entry, had received antibiotic therapy for more than 1 day before admission, or were enrolled at a time when no studies were being conducted, and one patient was not included because the dexamethasone was given orally. A final total of 97

Accepted for publication August 28, 1991.

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Table 1.—Patient Characteristics on Admission to the Hospital*

Characteristic	Treatment Groups	
	Steroid (n=41)	No Steroid (n=56)
Mean \pm SD age, y (range)	16.0 \pm 17.3 (2-72)	20.8 \pm 32.8 (2-180)
Age <6 mo	14 (34)	22 (39)
Sex		
M	21	28
F	20	28
Race or ethnic group		
White	21	22
Black	10	20
Hispanic	8	13
Other	2	1
Estimated duration of meningeal symptoms before admission, h	39.7 \pm 22.9	39.5 \pm 38.8
Pretreatment with oral antibiotics	13 (32)	12 (22)
Seizures before admission	13 (32)	11 (20)
Coma on admission	6/39 (15)	7/53 (13)
Shock on admission	3/40 (8)	5/55 (9)
Sepsis syndrome on admission	12/40 (30)	22/55 (40)
Relatively penicillin-resistant organisms	2/41 (5)	0/56 (0)

*Values are mean \pm SD or number of patients/total number (percent). There were no statistically significant differences in characteristics between treatment groups.

patients were included in the study, all of whom received therapy for a minimum of 10 days with cefotaxime, ceftriaxone, cefuroxime, ampicillin, or penicillin or more than one of these drugs. Thirty-nine patients received parenterally administered dexamethasone (0.15 mg/kg per dose every 6 hours for 4 days), one received methylprednisolone for 7 days, and one patient was given dexamethasone for 2 days.

Patients were given dexamethasone as having pneumococcal meningitis based on their clinical condition and results of CSF examination and a CSF culture that yielded *S pneumoniae* in 92 cases. If the patient was pretreated with parenterally administered antibiotics, either a positive blood culture or a positive CSF latex agglutination test result was required. Cerebrospinal fluid samples obtained at diagnosis and approximately 24 hours later from most patients were sent to the laboratory for routine tests and culture.

Management of patients was consistent throughout the 6-year study period. Patients underwent neurologic examinations daily while in the hospital, 6 weeks after discharge, and again at the 4- to 12-month follow-up visit or later. A brain-stem evoked response (BSER) audiologic examination was performed when therapy was discontinued and again 2 to 6 months later if results were abnormal. The BSER audiograms were interpreted by experienced pediatric audiologists. An absence of wave V response at 30 to 40 dB was considered mild, at 50 to 60 dB was considered moderate, at 70 dB was considered moderate-severe, at 80 to 100 dB was considered severe, and at greater than 100 dB was considered severe-profound hearing loss.^{12,13} Only bilateral

Table 2.—Hospital Course and Response to Therapy for Patients in the Two Treatment Groups*

Characteristic	Treatment Groups		P
	Steroid (n=41)	No Steroid (n=56)	
Fever duration, d	2.6 \pm 2.7	3.6 \pm 3.3	.035
Incidence of 2° fever	14/27 (38)	10/50 (20)	.11
Thrombocytopenia†	9/39 (23)	9/55 (16)	.58
Anemia‡	27 (66)	32 (57)	.51
Hypocalcemia§	4 (10)	5 (9)	1.0
Hyponatremia	8/39 (21)	15/55 (27)	.61
Relative neutropenia¶	6 (15)	5/55 (9)	.52
Seizures	19 (46)	22/55 (40)	.68
Subdural effusions	7 (17)	9 (16)	.88
Hydrocephalus	1 (2)	2 (4)	1.00
Positive blood culture	33/35 (94)	42/46 (91)	.69
Positive cerebrospinal fluid culture at 24-48 h	2/30 (7)	0/35 (0)	.21
Deaths during treatment	4 (10)	5 (9)	1.00

*Values are mean \pm SD or number of patients/total number (percent).

†Thrombocytopenia was defined as platelet count less than $150 \times 10^9/L$.

‡Anemia was defined as a hemoglobin or hematocrit value less than 2 SDs from the mean for age.

§Hypocalcemia was defined as a serum total calcium level less than 2.24 mmol/L.

||Hyponatremia was defined as a serum sodium value less than 130 mmol/L.

¶Relative neutropenia was defined as a white blood cell count less than 2 SDs from the mean for age or equivalent neutrophil count.

moderate or greater sensory neural hearing loss was considered evidence of substantial hearing loss.

Because BSER audiograms were not obtained in 12 patients, the physicians' findings of speech and language acquisition and grossly normal hearing in the patients at 4 years or longer after diagnosis were considered evidence that substantial permanent hearing loss had not occurred.

Statistical analyses were performed to detect differences between independent group proportions with a χ^2 or Fisher's Exact Test and between means with a Student t test or Mann-Whitney U test, when appropriate.¹⁴ Only two-tailed P values less than or equal to .05 were considered significant.

RESULTS

Patient Characteristics

Among the 97 patients, 44% were white, 32% were black, 22% were Hispanic, and 2% were other races, reflecting the general patient population served by the two hospitals in Dallas. The male-to-female ratio was 1:1. Sixty-four percent of the patients were younger than 1 year, and only 18% were older than 2 years. Forty-six patients had concomitant otitis media, seven had pneumonia, one had buccal cellulitis, one had periorbital cellulitis, two had maxillary sinusitis, and one had suppurative arthritis. No differences were noted in case-fatality rates or in neurologic outcome in those who presented with a focus of infection in addition to the central nervous system compared with those who did not.

On admission, 34 patients had evidence of sepsis syndrome as defined by Jacobs et al¹⁵ and modified for age

(Table 1). On admission or shortly thereafter, approximately 8% of the patients had septic shock, defined as the presence of sepsis syndrome and a blood pressure less than 2 SDs from the mean for age.

Forty-one patients received parenteral corticosteroid therapy in addition to antibiotic therapy, 13 of whom had been enrolled in one of the randomized, placebo-controlled trials.^{12,13} Fifty-six patients did not receive steroid therapy, 14 of whom had been enrolled in one of the placebo-controlled trials. From 1984 through 1987, 10 of the 41 steroid-treated and 44 of the 56 non-steroid-treated patients were examined ($P < .001$). The only treatment difference identified in those admitted earlier in the study was that a larger number were initially treated with ampicillin or penicillin plus chloramphenicol or with cefuroxime compared with cefotaxime or ceftriaxone, which were used later. All of the 35 non-steroid-treated and 28 of the 30 steroid-treated patients who underwent second lumbar punctures had sterile CSF cultures after 24 hours of therapy (Table 2). There were no statistically significant differences between steroid- and non-steroid-treated patients with regard to clinical and laboratory characteristics on admission to the hospital (Table 1). Two patients had relatively penicillin-resistant organisms (minimum inhibitory concentration, 0.1 to 1.0 $\mu\text{g/mL}$) and had received several courses of orally administered β -lactam antibiotics for recurrent otitis media before admission. Both were treated with parenterally administered cephalosporin from the outset, and follow-up CSF cultures at approximately 24 hours after diagnosis were sterile.

Hospital Course and Response to Therapy

Dexamethasone administration was associated with a marked reduction in total duration of fever, defined as a maximal rectal temperature greater than 38.2°C after the day of admission (Table 2). There were no significant differences between steroid- and non-steroid-treated patients with regard to routine laboratory studies, presence of seizures, subdural effusions, hydrocephalus requiring a shunt, positive second CSF cultures 24 to 48 hours after the onset of treatment, or case-fatality rates in the hospital (Table 1).

Results of the CSF examinations at the time of admission were similar for the two groups; at 24 to 48 hours, however, those who received dexamethasone therapy had a significantly higher mean (\pm SD) glucose concentration compared with that in non-steroid-treated patients (3.8 ± 1.4 vs 2.2 ± 1.1 mmol/L, $P < .001$). The mean protein concentrations in the second CSF samples of steroid-treated patients were lower than those of non-steroid-treated patients, but the difference was not statistically significant (0.87 ± 0.58 vs 1.0 ± 1.9 g/L, $P = .12$). The mean number of white blood cells in the second samples was similar for both groups.

Complications

Four patients each in the steroid- and non-steroid-treated groups had clinically evident gastrointestinal bleeding, and three patients in each group required a blood transfusion. However, two patients in each group had evidence of blood loss before diagnosis and treatment. Two patients with gastrointestinal bleeding died; both were from the non-steroid-treated group. One death was related to disseminated intravascular coagulation, and in the other death, neurologic deterioration occurred

after the first parenteral antibiotic dose. All patients with clinically apparent gastrointestinal bleeding had an altered sensorium, either semicomatose or comatose, on admission, and all but one had evidence of sepsis syndrome or septic shock, as defined previously.¹⁵

Cerebrovascular Instability.—Five (14%) of 35 assessable patients in the steroid-treated group and 16 (31%) of 52 assessable patients in the non-steroid-treated group ($P = .132$) developed evidence of cerebrovascular instability after initiation of parenteral antibiotic therapy. Cerebrovascular instability was defined as a change in neurologic and/or cardiovascular condition within 6 hours of initiation of parenteral antibiotic therapy and included a change in cardiovascular vital signs from normal for age to meeting the definition of sepsis syndrome/shock,¹⁵ a change in neurologic condition from being alert to semiconscious, or the development of a first seizure. All five of the steroid-treated patients developed cerebrovascular instability after the start of antibiotic therapy and before the first dose of steroid was administered. By contrast, none of 30 patients who received steroid therapy before or concurrently with antibiotic therapy developed cerebrovascular instability (0 of 30 vs 16 of 52 treated with antibiotics alone, $P = .0003$).

Nine (9%) of 97 patients died during hospitalization, four in the steroid-treated group and five in the non-steroid-group (Table 2). Two other patients died, one at 2 months and the other at 6 months after completion of treatment; neither had received steroid treatment. Death occurred significantly more often in patients who developed cerebrovascular instability (24% [5/21] vs 1.5% [1/68]; $P = .0025$).

Overwhelming Meningeal Infection.—Twenty-seven patients had evidence of overwhelming meningeal infection, defined by a white blood cell count less than $0.075 \times 10^9/\text{L}$ of CSF and more than an average of 10 organisms per high-power field on gram-stained smears of CSF observed at the time of diagnosis.^{16,17} These patients were sicker than those without evidence of overwhelming meningeal infection, as indicated by laboratory studies, altered states of consciousness, and the presence of septic shock, cerebrovascular instability, and gross gastrointestinal bleeding (Table 3). They accounted for two thirds of the deaths and had a significantly increased incidence of seizures and permanent bilateral moderate or greater hearing loss. Of the survivors of overwhelming meningeal infection, one of eight steroid-treated patients compared with seven of 13 non-steroid-treated patients had moderate or greater bilateral hearing loss ($P = .085$). The one steroid-treated patient had severe neurologic damage and BSER evidence of bilateral hearing loss before dexamethasone therapy was administered 31 hours after the first parenteral dose of antibiotic.

Neurologic Outcome

There was a consistent trend of fewer neurologic abnormalities in the steroid-treated group on examinations at 6 weeks and 6 months after illness (Table 4). In addition, bilateral moderate or greater hearing loss occurred less often in steroid-treated patients compared with non-steroid-treated patients ($P = .13$).

There were significantly fewer patients with an overall adverse neurologic outcome, including hearing impairment, in those who received steroid therapy compared with those who did not (four [11%] of 35 vs 14 [33%] of 43; $P = .033$) (Table 4). The presence of seizures controlled

Table 3.—Characteristics of Patients With Overwhelming Meningeal Infection in Pneumococcal Meningitis*

Characteristic	Overwhelming Meningeal Infection		P
	Present (n = 27)	Absent (n = 65)	
Steroid therapy	11 (41)	28 (43)	.98
Admission cerebrospinal fluid white blood cell count, $\times 10^6/L$	0.216 ± 0.210	3.087 ± 3.770	<.001
Coma	8 (30)	5/60 (8)	.024
Altered state of consciousness†	22 (81)	25/60 (42)	.001
Shock	6 (22)	2/63 (3)	.008
Cerebrovascular instability	10/25 (40)	10/61 (16)	.038
Gastrointestinal bleeding	5 (19)	3 (5)	.045
Relative neutropenia	7/26 (27)	3 (5)	.005
Thrombocytopenia	10/26 (38)	7 (11)	.006
Seizures	19 (70)	20/64 (31)	.001
Died in hospital	6 (22)	3 (5)	.017
Long-term neurologic sequelae	4/20 (20)	5/54 (9)	.241
Bilateral moderate or greater hearing loss	8 (30)	4/56 (7)	.016
Total adverse outcome‡	9 (33)	8/56 (14)	.085

*Values are number of patients/total number (percent) or mean \pm SD. The definitions of some characteristics are given in Table 1 or the text. "Overwhelming meningeal infection" is defined in Scheld et al,¹⁶ Weiss,¹⁷ or the text.

†Altered state of consciousness includes lethargy with decreased responsiveness, semiconsciousness, and coma.

‡Total adverse outcome includes patients with one or more neurologic abnormalities, including bilateral moderate or greater hearing loss.

by medication and isolated hydrocephalus in patients who had normal motor and intellectual development were not included in these figures.

COMMENT

The use of systemic corticosteroids as adjunctive therapy for bacterial meningitis in infants and children was shown in double-blind, placebo-controlled trials in Dallas and Costa Rica to modulate meningeal inflammation and lumbar CSF pressure and to substantially improve long-term outcome in those with disease caused principally by *H influenzae*.^{12,13} Because of the inevitable reduction in the incidence of *H influenzae* meningitis resulting from vaccination with the conjugated *Haemophilus* vaccines in early infancy, it is likely that a predominance of pneumococcal meningitis will be seen in the future. The paucity of data concerning dexamethasone therapy in these latter patients prompted our review of the Dallas experience with steroid treatment for pneumococcal meningitis.

Table 4.—Neurologic and Audiologic Outcome in Infants and Children With Pneumococcal Meningitis*

Characteristic	Treatment Groups		P
	Steroid (n = 37)†	No Steroid (n = 49)†	
Neurologic‡			
6-wk follow-up	3/34 (9)	6/38 (16)	.49
4-6 mo or longer follow-up	2/35 (6)	7/43 (16)	.18
Audiologic§			
Bilateral moderate or greater hearing loss	3/35 (9)	10/47 (21)	.14
Total adverse outcome	4/35 (11)¶	14/43 (33)¶	.033

*Values are number with sequela/number examined (percent).

†Numbers represent survivors who were available for follow-up.

‡Excludes hearing impairment, transient ataxia, and seizures controlled by medication.

§Patients with abnormal brain-stem evoked response examination results at discharge or at 6 weeks' follow-up were reexamined at 4 to 6 months or later to confirm impairment (see text).

||Includes patients with one or more neurologic abnormalities, including bilateral moderate or greater hearing loss.

¶Three patients received dexamethasone sodium phosphate therapy more than 24 hours after initiation of antibiotic treatment. If they are excluded from analysis (see text), the rates of total neurologic sequelae were three (9%) of 32 vs 14 (33%) of 43 ($P = .025$) for steroid- and non-steroid-treated patients, respectively.

Because the basic pathophysiologic mechanisms of meningeal inflammation in experimental pneumococcal and *Haemophilus* meningitis are similar,^{3,5,6,8,17,18} it was not surprising that dexamethasone had similar antiinflammatory effects in both models, as determined by CSF pressure, brain edema, cytokine concentrations, and the conventional CSF indexes of inflammation.^{5,19} This was also the case in our analysis of the effects of corticosteroid treatment on CSF inflammatory indexes and CSF interleukin 1 β and tumor necrosis factor α concentrations in patients with pneumococcal and *Haemophilus* meningitis enrolled in the placebo-controlled, double-blind trials.^{12,13}

The results of our retrospective study suggest strongly that corticosteroid therapy, especially when administered within 24 hours of starting parenteral antibiotic therapy, benefits neurologic and audiologic outcome in infants and children with pneumococcal meningitis. The percentage of survivors with any adverse outcome was markedly smaller in patients given steroid therapy within 24 hours of initiating parenteral antibiotic therapy compared with those who never received steroid therapy (three [9%] of 32 vs 14 [33%] of 43; $P = .025$). It also appeared that steroid-treated patients with overwhelming pneumococcal meningeal infection^{16,17} fared better on follow-up neurologic and audiologic examinations and that fewer steroid-treated patients developed evidence of cerebrovascular instability after initiation of parenteral antibiotic therapy compared with non-steroid-treated patients (0 of 30 vs 16 [31%] of 52; $P = .0003$). Five steroid-treated patients developed cerebrovascular instability before steroids were administered, underscoring the importance of providing steroid therapy before or concurrently with antibiotic therapy.^{9,13} Our results are consistent with those of Girgis et al,²⁰ who demonstrated markedly lower rates of death and hearing impairment in 52 dexamethasone-treated

compared with 54 non-steroid-treated children, adolescents, and adults with pneumococcal meningitis.

However, the data substantiating a beneficial effect on outcome from meningitis caused principally by *H influenzae* were derived from prospective, double-blind, placebo-controlled trials,^{12,13} whereas the data from our study were retrospectively gathered, although more than half of the patients had been prospectively enrolled in therapeutic trials.^{12,21} Although a placebo-controlled, double-blind study of dexamethasone therapy in pneumococcal meningitis would be ideal, we believe that the risk-benefit ratio is favorable and that dexamethasone therapy should be considered for use in infants and children with pneumococcal meningitis until results of such a study, if undertaken, are available.

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Haemophilus b Disease After Vaccination With *Haemophilus b* Polysaccharide or Conjugate Vaccine

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● The reported frequency of invasive *Haemophilus influenzae* type b disease occurring within 1 year after immunization was compared in American children who received either Praxis Biologics' *Haemophilus b* polysaccharide vaccine or Connaught Laboratories' *Haemophilus b* conjugate vaccine during the first year of distribution. All domestic cases reported to the Food and Drug Administration or the Centers for Disease Control were included in the study. An estimated 4.5 million and 2.0 million doses of polysaccharide and conjugate vaccines were administered, respectively. Approximately three cases of early-onset disease (disease developing less than 15 days after vaccination) per million doses were reported for the polysaccharide compared with four cases per million doses for the conjugate vaccine. There were 30.7 reported vaccine failures per million doses of the polysaccharide vaccine compared with 9.0 per million doses of the conjugate vaccine, a 3.4-fold difference. The reporting rate ratios (cases of vaccine failure to cases of early-onset disease) for the polysaccharide and conjugate were 11.5 and 2.3, respectively, a fivefold difference. Thus, compared with recipients of the polysaccharide vaccine, vaccine failures reported among recipients of the conjugate vaccine were 80% fewer than expected. (AJDC. 1991;145:1379-1382)

Haemophilus influenzae is the causative agent of a spectrum of human diseases, the most serious of which is meningitis. Other invasive infections caused by this organism include pneumonia, epiglottitis, cellulitis, and septic arthritis. Nearly all invasive disease caused by *H influenzae* in children is due to capsular type b, one of six capsular types.¹ The estimated annual incidence of *Haemophilus b* disease in children younger than age 2 years in the United States is about 100 per 100 000.²

The low incidence of *Haemophilus b* disease in older

children and adults correlates with the presence of serum bactericidal antibodies.³ Antibodies to the type b capsular polysaccharide, which is composed of ribose ribitol phosphate, are bactericidal and opsonic.^{4,5} A 1974 efficacy trial with a *Haemophilus b* polysaccharide vaccine showed significant protection for children aged 18 months and older.⁶ Based on this finding, a *Haemophilus b* polysaccharide vaccine was licensed in April 1985 for use in children aged 24 months and older. However, protective effectiveness of the polysaccharide vaccine in the United States was less than expected.^{7,8} An improved polysaccharide-protein conjugate vaccine for protection against *H influenzae* type b was licensed in December 1987 for use in children aged 18 months and older.

Reporting of unexpected adverse events after administration of *Haemophilus b* vaccines has been strongly encouraged.⁹ Failure of vaccines to protect against *Haemophilus b* disease is a reportable adverse event. Adverse events are generally reported to the Food and Drug Administration (FDA), but may be reported to the Centers for Disease Control (CDC). Reports submitted to the FDA are primarily from manufacturers or health care providers¹⁰ and are entered into the Spontaneous Reporting System, a computerized database. Adverse events reported to the FDA and CDC were used in an earlier study¹¹ to describe the spectrum of disease due to *H influenzae* type b occurring in polysaccharide-vaccinated children.

In this study, we compare the frequency of reported invasive disease occurring within 1 year after immunization in American children who received either the *Haemophilus b* polysaccharide (PRP, Praxis Biologics Inc, Rochester, NY) or the *Haemophilus b* conjugate (PRP-D, Connaught Laboratories Inc, Swiftwater, Pa) vaccine any time during the first year of the products' distribution. The first year was chosen for both products because during this time only one manufacturer's product was on the market.

PATIENTS AND METHODS

The first year of distribution of PRP was defined as May 1, 1985, through April 30, 1986, and the first year for PRP-D was defined as January 1, 1988, through December 31, 1988. Children vaccinated in the United States during these times who developed *Haemophilus b* disease within 1 year of immunization were eligible for our study and were included if their disease was reported to the FDA or CDC. Thus, each vaccinated child was allotted equal time (365 days) to develop disease. In a similar study by Nelson and Granoff,¹² this was

Accepted for publication August 30, 1991.

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Table 1.—*Haemophilus b* Disease Occurring Within 1 Year of Immunization With Connaught Laboratories' *Haemophilus b* Conjugate Vaccine*

Patient No.	Sex	No. of Days Between Vaccination and Disease Onset	Disease	State	Age at Immunization, mo	Surveillance
1	M	1	Septicemia	Minn	32	A
2	M	2	Meningitis	Wash	18	P
3	F	2	Meningitis	Calif	29	A
4	M	3	Cellulitis	Mich	17	P
5	F	4	Septicemia	Ga	26	P
6	F	4	Meningitis	Ore	23	P
7	M	6	Meningitis	Ohio	20	P
8	M	14	Meningitis	Mass	18	P
9	M	25	Meningitis	Calif	19	P
10	M	35	Meningitis	Pa	19	P
11	F	50	Meningitis	Conn	19	A
12	F	59	Meningitis	Mont	17	P
13	F	65	Meningitis	Calif	27	A
14	NS	91	Pneumonia	Wis	18	P
15	M	116	Meningitis	Fla	15	P
16	M	119	Septicemia	Calif	46	A
17	NS	128	Meningitis	Tenn	37	A
18	NS	140	Meningitis	Ill	18	P
19	NS	143	Cellulitis	Okla	23	A
20	F	174	Meningitis	Calif	18	A
21	NS	176	Cellulitis	Calif	18	A
22	M	220	Septicemia	Tex	29	A
23	F	261	Cellulitis	Minn	23	A
24	F	290	Meningitis	Calif	18	A
25	F	321	Meningitis	Tenn	19	A
26	M	353	Epiglottitis	Okla	23	A

*NS indicates not specified; A, active; and P, passive. Included under active surveillance are six reports from the Centers for Disease Control and eight reports from parts of the United States considered to be under more active surveillance than usual.

not the case, as only those vaccinated children who developed disease within the first 13 months of distribution of the applied vaccine could have been included if their disease had been reported. Thus, children vaccinated 10 months into a vaccine's first 13 months of distribution would have to have developed disease in 3 months to be included in their study.

Other study methods and case definitions are as described by Hiner and Frasch.¹¹ Cases of disease developing in children less than 15 days after immunization were counted as early-onset cases of the disease, not as vaccine failures. The child's age at immunization was determined when possible from the date of birth and was recorded as the last full month of age. When the birth date was not available, the age at vaccination indicated on the report was used. The number of days between vaccination and disease onset was calculated based on the reported dates of immunization and hospital admission. The two manufacturers provided estimates of amounts of vaccine distributed and administered.

RESULTS

There were 150 cases of *Haemophilus b* disease reported in children who received PRP, and these 150 cases are a subset of cases presented in our earlier paper.¹¹ Twenty-six cases of *Haemophilus b* disease were reported after immunization with PRP-D (Table 1). Another case of early-onset disease was reported after PRP-D vaccination in a 19-

month-old infant, but was not included because the child resided in British Columbia. Twenty cases (77%) were reported by physicians and/or the manufacturer, but, of these, eight were considered to be from areas of active surveillance.^{8,13-15} Six reports (23%) obtained from the CDC were from an active surveillance study of meningitis.¹⁶ In comparison, 16 (11%) of 150 reports of cases of disease after PRP vaccination originally reported by Granoff et al¹⁷ were from active surveillance studies. Two (25%) of the eight PRP-D-associated cases of early-onset disease and 12 (67%) of 18 PRP-D vaccine failures were considered to have been reported from areas of active surveillance. There were no cases of early-onset disease associated with PRP among the active surveillance reports.

Approximately 60% of cases of both early-onset disease and vaccine failure after receipt of PRP-D involved meningitis compared with 54% of cases of PRP vaccine failures (Table 2). Approximately 75% fewer cases of epiglottitis developed in patients with PRP-D vaccine failure (6%) compared with patients with PRP vaccine failure (25%). There was no important difference between the mean or median age at immunization of children who experienced early-onset disease or vaccine failures in the PRP or PRP-D groups, but there

was a median age difference of 6 months between administration of the two vaccines (Table 3).

Table 4 compares the rates of reported *Haemophilus b* disease within 1 year after immunization with PRP and PRP-D. Praxis Biologics reported that during the first year of distribution approximately 4.5 million doses of PRP had been administered (about 70% of distributed vaccine). Connaught Laboratories reported that 2.0 million doses of PRP-D had been administered during its first year (about 60% of distributed vaccine). There were 2.7 reported cases of early-onset disease per million doses of PRP compared with 4.0 cases per million doses of PRP-D. The rate of reported PRP-D vaccine failures was about 30% that of PRP. The reporting rate ratios (cases of vaccine failure to cases of early-onset disease) for PRP and PRP-D were 11.4 (30.7:2.7) and 2.3 (9.0:4.0), respectively, demonstrating a fivefold difference. Excluding reports from active surveillance areas for both vaccines resulted in a 10.2-fold difference in the rate ratios.

Table 2.—Distribution of Disease in Patients With Early-Onset Disease and Vaccine Failures After *Haemophilus b* Vaccination*

Disease	Polysaccharide		Conjugate	
	Early-Onset Disease	Vaccine Failure	Early-Onset Disease	Vaccine Failure
Meningitis	4 (33)	75 (54)	5 (62)	11 (61)
Epiglottitis	3 (25)	34 (25)	0	1 (6)
Cellulitis	1 (8)	10 (7)	1 (13)	3 (17)
Pneumonia	0	8 (6)	0	1 (6)
Bacteremia	2 (17)	6 (4)	2 (25)	2 (11)
Other	2 (17)	5 (4)	0	0
Total	12 (100)	138 (100)	8 (100)	18 (101)

*Values are number (percentage) of cases developing less than 15 days after vaccination. Percentages may not total 100 owing to rounding.

Table 3.—Age at Immunization of Vaccinated Children Who Later Developed *Haemophilus b* Disease

Vaccine	Age at Immunization, mo					
	Early-Onset Disease			Vaccine Failure		
	Median	Mean	Range	Median	Mean	Range
Polysaccharide	24	27.4	22-41	25	29.1	16-60
Conjugate	22	22.2	17-32	19	22.8	15-47

Table 4.—Comparison of Reported Rates of *Haemophilus b* Disease in Children Who Received Polysaccharide or Conjugate Vaccine During the First Year of the Vaccine's Distribution

Vaccine	No. of Doses Distributed, Millions	No. of Doses Administered, Millions (% of Doses Distributed)	<i>Haemophilus b</i> Disease, No. of Cases Per Million Doses (No. of Cases)			
			Early-Onset Disease	Vaccine Failure	Total	Rate Ratio*
Polysaccharide	6.4	4.5 (70)	2.7 (12)	30.7 (138)	33.4 (150)	11.4
Conjugate	3.3	2.0 (61)	4.0 (8)	9.0 (18)	13.0 (26)	2.3

*Ratio of rate of vaccine failure to rate of development of early-onset disease.

COMMENT

We compared the frequency of reported *Haemophilus b* disease occurring within 1 year after immunization in children vaccinated with either PRP or PRP-D anytime during the first year of the vaccines' distribution when PRP was the only *Haemophilus b* vaccine available and when PRP-D was the only *Haemophilus b* conjugate available. Cases were reported from both active and passive surveillance systems. Because the dynamics of reporting in these two systems are different, examining their separate effects was important. By excluding reports from active surveillance, the reporting rate ratio difference increased from fivefold to tenfold. We also noted that cases occurring more than 3 months after immunization with PRP-D were much more likely to be reported by active surveillance.

The median age at immunization for the PRP and PRP-D vaccine recipients who experienced vaccine failure was 25 months and 19 months, respectively, but it is unclear whether this difference can fully account for the lower incidence of epiglottitis after vaccination with PRP-D. The peak age for occurrence of epiglottitis is approximately 30 months.¹⁸

In an approach similar to that of Nelson and Granoff,¹² but using reporting rates rather than reported numbers, we determined that the reported rate of vaccine failures in PRP-D recipients would have to be 46.0 per million doses administered for the vaccine failure-early-onset disease rate ratios in PRP-D and PRP recipients to be the same (PRP-D, 46.0:4.0 [11.5]; PRP, 30.7:2.7 [11.4]). Given the number of PRP-D doses administered (2.0 million), the rate of 46.0 per million would correspond to 92 vaccine failures among those who received PRP-D. However, only 18 cases were reported, or 80% fewer than expected. These data and the 3.4-fold fewer vaccine failures per million doses suggest that PRP-D is more effective than PRP. These calculations are based on the assumption that no cases of early-onset disease result from the transient decrease in antibody that occurs in the first few days after immunization.¹⁹

Because underreporting of cases of both early-onset disease and vaccine failure is certain and the number of vaccine doses administered is an approximation, the derived reporting rates of disease after immunization are only crude estimates of the true incidence. The reporting rate ratios, however, remain unchanged even if vaccine exposure changed because both the numerator and the denominator of the rate ratio are equally affected. Underreporting becomes a more important issue in considering potential biases in this study.

Potential biases include a relative overreporting of early-onset disease after PRP-D vaccination or a relative

underreporting of PRP-D vaccine failures. Given the nature of invasive *Haemophilus b* disease, it is unlikely that PRP-D-associated cases of early-onset disease would be preferentially reported compared with PRP-associated cases. Regarding the latter bias, given the extent of publicity and discussion in the last half of 1987 and into 1988 after studies of the efficacy of the PRP vaccines,^{7,8} heightened interest in the efficacy of the conjugate vaccines would likely have stimulated reporting of vaccine failures. Thus, comparative underreporting of PRP-D vaccine failures seems unlikely. However, such a bias might have existed if children vaccinated with PRP-D had been allotted less time to develop disease than children vaccinated with PRP. This could have occurred if (1) to be included in the study, vaccinated children who developed disease would have had to have experienced disease onset within the first year of distribution of the applied vaccine, and (2) PRP-D had been used more extensively during the last half of its first year of distribution than PRP was during its first distribution year. Importantly, the variation in overall use of PRP-D vs PRP during their first year of distribution did not have to be accounted for with our study design because all vaccinated children were allotted 365 days to develop disease.

The first conjugate vaccine, PRP-D, was introduced in 1987. It was licensed based on its superior immunogenicity compared with PRP. The reported effectiveness of PRP in American children has been estimated in a series of postmarketing case-control studies.^{7,8,20} The effectiveness estimates ranged from 50% to 88% for most of these studies. Recent case-control studies of PRP-D have shown its effectiveness to be 100% (95% confidence interval [CI], 72% to 100%) in Minnesota²¹ and 88% (95% CI, 49% to 97%) in Los Angeles County, California.¹⁵

Based on the data presented and considering potential reporting biases, the PRP-D conjugate vaccine appears to be more effective than the polysaccharide in children aged 18 months or older. This is consistent with the results of the above cited case-control studies. *Haemophilus b* conjugate vaccines produced by Praxis Biologics and Merck Sharp & Dohme, West Point, Pa, have been recently licensed for use in children beginning at age 2 months.²²

We thank Jay Wenger, MD, Special Pathogens Branch, Centers for Disease Control, Atlanta, Ga, for providing reports of *Haemophilus b* disease in vaccinated children.

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Comparison of Maternal and Newborn Serologic Tests for Syphilis

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• **Objective.**—To compare the cord blood, newborn serum, and maternal serum for the diagnosis of congenital syphilis. **Design.**—Retrospective chart review.

Setting.—Kings County Hospital Center, Brooklyn, NY.

Patients.—Three hundred forty-eight mother-newborn pairs with positive syphilis serology.

Measurements and Results.—One hundred fifteen newborns (33%) had rapid plasma reagin tests of cord blood that were nonreactive. Their mothers had positive serologic findings. There were 10% false-positive cord blood samples (cord blood rapid plasma reagin tests reactive, newborn serum rapid plasma reagin tests nonreactive) and 5% false-negative cord blood samples (cord rapid plasma reagin tests nonreactive, newborn serum rapid plasma reagin tests reactive). Thirty-three newborns had congenital syphilis. Seven newborns had cord titers fourfold higher than their mothers'; only four of these newborns had congenital syphilis. Maternal serology is superior to cord blood analysis for identifying newborns at risk of congenital syphilis. (AJDC. 1991;145:1383-1388)

Congenital syphilis has reached epidemic proportions in New York State. In response to this outbreak, the state requires that all newborns have their cord blood tested for syphilis.¹ According to state law, maternal blood tested at delivery is an acceptable alternative to cord blood. Do the two samples provide similar information? Only limited comparisons of mother's and newborn's serology results at delivery^{2,3} are available. These studies suggest that cord blood serology is inferior to maternal blood serology for the detection of congenital syphilis.

Although there is said to be a large experience with serology results in the diagnosis of congenital syphilis, recommendations and statements about syphilis serology results in the newborn period are based on anecdotal information and unpublished data. For instance, the Centers for Disease Control, Atlanta, Ga, suggests syphilis serologic testing on a newborn's serum rather than on the cord blood because of fewer false-positive results on serum

samples,⁴ but data are not available to support or refute these findings. A recently adopted diagnostic criterion for congenital syphilis⁵ is a newborn's titer that is four times as great as that of the maternal titer at delivery. Evidence for the usefulness of this ratio has not been published.

Because only limited studies or anecdotal information on the association between cord blood and maternal blood syphilis serologies were available, cord blood, maternal serum, and newborn serum syphilis serology results were reviewed at this institution to determine if (1) a rapid plasma reagin test (RPR; Becton Dickinson Microbiology Systems, Cockeysville, Md) performed on cord blood identified newborns with congenital syphilis, (2) the ratio of newborn cord blood RPR to maternal blood RPR was helpful in the diagnosis of congenital syphilis, and (3) an RPR performed on newborn serum was superior to an RPR performed on cord blood.

PATIENTS, MATERIALS, AND METHODS

In Kings County Hospital Center, Brooklyn, NY, an RPR test is performed on the cord blood of almost all newborns and on blood obtained from almost all mothers at delivery. A positive RPR is confirmed with the use of a fluorescent treponemal antibody absorption test (FTA-ABS; Clinical Sciences, Whippany, NJ). Quality control of the RPR test is performed twice a day. The RPR test was reproducible within one tube dilution when 2 months' of tests were reviewed.

All RPR tests performed on women who gave birth at Kings County Hospital from January 1988 to November 1989 were reviewed. Mother-newborn pairs were identified by finding a positive RPR in any serum specimen from either member of the pair. Specimens that were sent for RPR testing were maternal serum, newborn's cord blood, or serum of a newborn during the first days of life. Additional newborn testing was only done on a second newborn serum specimen and not further testing of the serum from the clotted cord blood. The diagnosis of congenital syphilis was based on the following modified guidelines established by the Centers for Disease Control:^{5,6}

The definition for congenital syphilis includes confirmed or presumptive categories. The Centers for Disease Control defines confirmed cases of congenital syphilis as infants in whom *Treponema pallidum* is identified by dark-field microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material. The Centers for Disease Control defines presumptive cases of congenital syphilis as either of the following:

A. An infant whose mother had untreated or inadequately treated syphilis at delivery, regardless of findings in the infant; or

Accepted for publication July 22, 1991.

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B. Any infant or child who has a reactive treponemal test for syphilis and any one of the following:

1. any evidence of congenital syphilis on physical examination (signs in an infant less than age 2 years may include hepatosplenomegaly, characteristic skin rash, condyloma lata, snuffles, jaundice (syphilitic hepatitis), pseudoparalysis, or edema (nephrotic syndrome); or

2. any evidence of congenital syphilis on long-bone radiograph; or

3. reactive cerebrospinal fluid (CSF) VDRL; or

4. elevated CSF cell count or protein level (without other cause); or

5. quantitative nontreponemal serologic titers that are fourfold higher than the mother's (both drawn at birth); or

6. reactive test for FTA-ABS-19S-IgM antibody.

The definition of congenital syphilis used in this study included only confirmed and presumptive B:1,2,3 categories. Newborns were included in group B1 with any of the following signs or symptoms: hepatosplenomegaly, hepatitis, characteristic rash, or lymphadenopathy. *Hepatitis* was defined as hyperbilirubinemia with an indirect bilirubin level greater than 17 $\mu\text{mol/L}$, or an aspartate aminotransferase level greater than 75 U/L. Newborns were not excluded from the diagnosis of congenital syphilis if they had nonreactive (NR) cord blood titers. A diagnosis of congenital syphilis was not made on the inadequacy of maternal therapy alone (presumptive group A) since only some of these newborns have congenital syphilis. Categories B:4, 5, and 6 were also excluded. Category B4 was excluded since the values given for abnormal CSF white blood cell count ($>0.005 \times 10^9/\text{L}$) and protein level ($>0.40 \text{ g/L}$)⁵ are well within normal for newborns.⁷ Category B5 was excluded since this definition was being evaluated. Category B6 was excluded since no newborns had this test performed.

The diagnosis of confirmed congenital syphilis was made based on a positive immunofluorescence test for *T pallidum* using rabbit antiserum in an indirect immunofluorescent antigen test. After November 1988, all newborns born to mothers with positive RPRs received parenteral penicillin (either intravenous penicillin G or intramuscular penicillin G procaine) for 10 days.

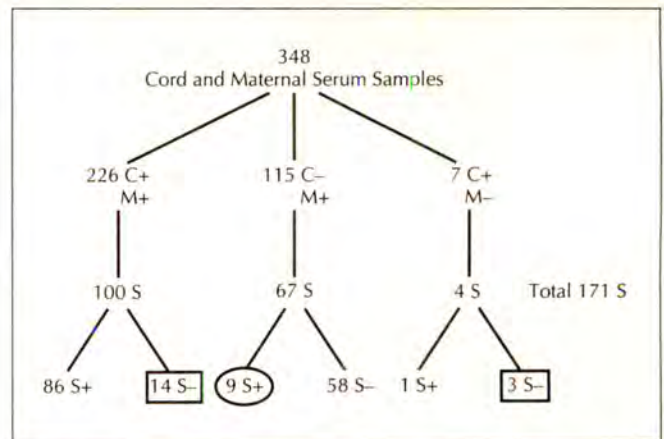
RESULTS

Of the 9421 newborns born during the 22-month study period, there were 429 (5%) mother-newborn pairs with positive RPR results in either one of the pair. Four hundred eight had medical records available for review. Twenty-eight were excluded from analysis because the FTA-ABS was either negative (11) or not done (17), leaving 380 (89%) mother-newborn pairs with positive FTA-ABS results. Of the 380 pairs, 14 (3.7%) had discordant FTA-ABS results between members of the pair but were still included in the analysis.

Only 348 (91.6%) of the 380 mother-newborn pairs could be evaluated for comparison of maternal and newborn serologic findings since five newborns had no cord blood samples sent for analysis, and 27 mothers had no maternal serum samples sent for analysis. These 348 pairs were the basis for the analysis.

RANGE OF TITERS

The range of RPR titers seen in all specimens was similar: cord serum NR to 1:2048, newborn serum NR to 1:1024, and maternal serum NR to 1:1024. Significant discordance between titers was assumed, based on usual practice, if titers differed by more than or equal to two tube dilutions (fourfold). Analysis of the 348 mother-newborn pairs included 171 pairs where there were both newborn cord, serum, and maternal samples for comparison. The results for mother-newborn pairs with RPR-



Analysis of 348 cord and maternal serum samples. C indicates cord serum; M, maternal serum; S, newborn serum; plus sign, RPR (rapid plasma reagin) positive; minus sign, RPR nonreactive; boxed items, cord blood RPR false positives; and circled item, cord blood RPR false negatives.

positive results were analyzed separately from those with any RPR NR results (Figure).

Analysis of RPR-Positive Serum Samples

Comparison of RPR-Positive Cord and Maternal Serum Samples.—There were 226 (65%) pairs with RPR-positive cord and maternal serum samples (Table 1). The majority of cord blood samples (136 of 226 or 60%) were within two dilutions of maternal titer.

Comparison of RPR-Positive Newborn and Maternal Serum Samples.—One hundred seventy-one pairs of newborn serum and maternal titers were available for comparison, but only 95 (55.6%) of these newborn serum samples were RPR positive when maternal RPR was also RPR positive. The majority of the specimens (54 of 95 or 57%) were fourfold lower (two or more dilutions lower) than the maternal titer (Table 1).

Comparison of RPR-Positive Cord and Newborn Serum Samples.—Only 87 (51%) of 171 samples of both newborn cord and newborn serum were RPR positive. There were few differences between titers when both cord and newborn serum samples were RPR positive. Most (79 of 87 or 91%) cord and newborn serum samples were within two tube dilutions of each other. Three newborns had cord blood that was four times higher than the newborn serum titer, and five newborns had newborn serum that was four times higher than the cord titer.

Analysis of Serum Samples With RPR Nonreactive Samples

Comparison of Cord and Maternal Serum Samples Where One Sample Is Nonreactive.—There were 115 newborns (33%) whose cord blood samples were RPR NR when maternal serum samples were positive. There were seven newborns (2%) with RPR-positive cord blood samples whose mothers had RPR NR serum samples.

Comparison of Newborn Serum With Maternal Serum.—*Group With RPR NR Cord Blood Samples.*—Sixty-seven (58%) of the 115 newborns who had RPR NR cord blood samples and RPR-positive maternal serum had additional newborn serum samples sent for clarification of titers. Nine of these serum samples were RPR positive (Table 1). These nine included eight with newborn serum

Table 1.—Comparison of Fourfold Difference in RPR-Reactive Mother-Newborn Serum Sample Pairs*

	Fourfold Lower	Same†	Fourfold Higher	Total
Cord vs maternal	83 (12)	136 (13)	7 (4)	226 (29)
Serum vs maternal	54 (4)	39 (5)	2 (1)	95 (10)

*RPR indicates rapid plasma reagin. Numbers in parentheses denote newborns with congenital syphilis. Ten had serum samples taken that were RPR positive and a total of 29 had newborn cord and maternal serum samples that were RPR positive.

†Newborn titer within two tube dilutions of maternal titer.

samples two dilutions or more higher than the cord blood sample (1:2 to 1:32), and one with newborn and cord titers within two dilutions (newborn titer 1:1).

Group With RPR NR Maternal Serum.—There were seven newborns with positive cord RPR and NR maternal RPR. Additional newborn serum samples were sent for analysis on four newborns and only one remained positive (cord and newborn serum titer 1:16), with three becoming NR (cord titers 1:1 to 1:2). The mother's serum samples on these newborns were unavailable for further testing so it is unknown if any maternal specimens were NR due to the prozone phenomenon.

Group With RPR NR Newborn Serum.—The group with positive RPR in both maternal and cord serum samples had additional newborn serum samples sent for analysis on 100 (44%) of 226. Fourteen of these newborns, who initially had RPR-positive cord serum samples (titers 1:1 to 1:8), had additional newborn serum samples that were NR.

False-Positive and False-Negative Cord Serum Samples

If newborn serum specimens are taken to be the true-positive samples, then the number of false-positive cord RPR tests was 17 (10%) of 171. The number of false-negative cord RPR tests was nine (5%) of 171.

Newborns With Congenital Syphilis

Thirty-three newborns with congenital syphilis in the group of 348 pairs had cord and maternal titers available for comparison; of these, 13 had cord, newborn serum, and maternal titers available for comparison. Cord titers ranged from NR to 1:2048. However, after November 1988, all newborns at risk were treated for congenital syphilis; therefore, more newborns may have had congenital syphilis since asymptomatic newborns may not be detected with routine testing. Twenty-nine newborns had RPR-positive cord blood samples, and four newborns had RPR NR cord blood samples at delivery.

The diagnosis of congenital syphilis was made using the criteria already mentioned. Table 2 contains information on the newborns with congenital syphilis. Eleven newborns had only abnormal roentgenographic findings, five had only a positive CSF VDRL, and six had both findings. Some of these newborns also had other manifestations of congenital syphilis such as hepatosplenomegaly, rash, and hepatitis. Three newborns only had hepatosplenomegaly as their manifestation of congenital syphilis, and seven newborns had hepatitis as their sole manifestation of congenital syphilis. Four newborns had confirmed congenital syphilis, and 29 had presumptive congenital syphilis.

The four newborns with confirmed congenital syphilis had *T pallidum* identified with immunofluorescence techniques in either nasopharyngeal or umbilical smears. Two of these had positive CSF VDRL alone. One had a positive CSF VDRL and abnormal roentgenographic findings, and one had abnormal roentgenographic findings alone.

The four newborns with NR cord blood samples had findings compatible with presumptive congenital syphilis. Three of them had evidence of congenital syphilis at birth (patients 2, 19, and 32) and one did not (patient 16). The newborn who did not have evidence of congenital syphilis at birth (patient 16) had no additional newborn serum samples sent for analysis and was not evaluated for congenital syphilis at birth. The newborn received no therapy and returned at age 4 months with florid congenital syphilis and a titer of 1:512. This patient is the subject of a previous report.⁸ Comparison of RPR-positive infant and maternal titers is included in Table 1.

Analysis of Newborn Cord Serum Titer Four Times Higher Than Maternal Titer in RPR-Positive Specimens

Among newborns and mothers with positive syphilis tests, there were seven newborns whose cord serum titer was four times higher than their mothers' at delivery (Table 3). Only four of these had evidence of congenital syphilis. The other three did not have evidence of congenital syphilis; however, they did not undergo a full evaluation since none had roentgenograms performed, and only one had a lumbar puncture performed. Therefore, the number with congenital syphilis could have been higher. Another five newborns had cord serum titers four times higher than their mothers' (1:2 to 1:16), but their mothers had NR RPR serologic findings. None of these newborns had any evidence of congenital syphilis, and they were not included in the analysis of newborn cord serum titer four times higher than maternal titer since only one member of the pair had RPR-positive serologic findings.

All those with congenital syphilis whose titers were fourfold higher than their mothers' had titers of 1:1024 or greater. However, all newborns in the analysis with titers of 1:1024 or greater had congenital syphilis. Sensitivity and specificity of cord titer fourfold maternal titer are four (12%) of 33 and 312 (99%) of 315, respectively. The positive predictive value is four (57%) of seven and the negative predictive value is 312 (91%) of 341.

Analysis of Newborn Serum Titer Fourfold Maternal

Only three newborns had newborn serum titers fourfold higher than maternal titers. One newborn (Table 2, patient 10) had evidence of congenital syphilis. One newborn with newborn cord and serum titer of 1:16 and maternal titer RPR NR had no evidence of congenital syphilis. The third newborn had a cord titer of 1:16, serum titer of 1:128, maternal titer of 1:16, and no evidence of congenital syphilis; however, no roentgenograms were obtained.

COMMENT

These data confirm that RPR testing of newborn's cord serum fails to identify many mother-newborn pairs who are at risk for syphilis. One third of newborns whose mothers have positive syphilis serologic findings will have RPR NR cord blood samples. Our data are similar to those of Miller et al,² who, in 1960, found that 66% of 221 infants born to mothers with positive syphilis serologic

Table 2.—33 Newborns With Congenital Syphilis*

Patient No.	Rapid Plasma Reagin			Symptoms	Roentgenogram	CSF VDRL	IFA
	Cord	Serum	Maternal				
1	1:64	1:64	1:128	—	+	+	+
2	NR	NR	1:32	P	ND	—	ND
3	1:8	ND	1:32	P	—	—	ND
4	1:256	1:128	1:1024	—	—	+	+
5	1:512	1:512	1:512	R,H,S	ND	ND	ND
6	1:256	ND	1:256	—	+	ND	ND
7	1:64	1:64	1:256	H,P	ND	—	ND
8	1:64	1:64	1:128	—	+	+	ND
9	1:2048	ND	1:256	R,H,S,P	+	+	ND
10	1:1024	1:1024	1:256	—	+	+	—
11	1:64	ND	1:128	R,H,S,P,L	+	+	ND
12	1:32	ND	1:512	—	+	—	—
13	1:256	ND	1:256	H,S,P	+	+	ND
14	1:1	NR	1:2	—	+	—	+
15	1:64	ND	1:64	—	+	—	ND
16	NR	ND	1:16	—	ND	ND	ND
17	1:32	ND	1:256	H,P	+	ND	ND
18	1:8	1:2	1:32	H,P	—	ND	ND
19	NR	ND	1:2	P	ND	—	ND
20	1:32	ND	1:64	R,H,S	+	—	ND
21	1:16	1:16	1:128	—	ND	+	+
22	1:128	ND	1:1024	—	—	+	ND
23	1:64	ND	1:128	H,S,P	+	—	ND
24	1:4	ND	1:32	P	ND	—	ND
25	1:16	ND	1:128	R,H,S	+	—	ND
26	1:32	1:64	1:128	R,H,S	—	ND	ND
27	1:1024	ND	1:128	H,S	ND	ND	ND
28	1:2048	ND	1:64	R,H,S	—	+	ND
29	1:4	ND	1:32	P	—	—	ND
30	1:512	ND	1:512	H,S,P	+	—	ND
31	1:16	ND	1:32	—	ND	+	ND
32	NR	NR	1:8	—	+	ND	ND
33	1:8	1:8	1:8	—	+	ND	ND

*CSF VDRL indicates cerebrospinal fluid Venereal Disease Research Laboratory Test; IFA, immunofluorescent *Treponema pallidum* antigen detection test; NR, nonreactive; ND, not done; P, hepatitis; R, rash; H, hepatomegaly; S, splenomegaly; L, lymphadenopathy; plus sign, positive or abnormal; and minus sign, negative or abnormal.

findings had positive serologic tests for syphilis and/or *T pallidum* immobilizing antibody at birth.

While the aim of cord blood testing is to identify newborns with congenital syphilis, the real goal of the screening program should be to identify mothers with syphilis and therefore also their newborns. If the mother has syphilis then the newborn is at risk of congenital syphilis.

Many of these women do not have prenatal care,⁹ and their first screening for syphilis is at delivery. The hospitalization at delivery may be the only chance for treatment of the mother and prevention of further syphilitic pregnancies. Even if a woman has had prenatal care, one should not rely on a previous negative syphilis serologic finding during the pregnancy to determine maternal infection at delivery.¹⁰

Screening the mother's serum alone would miss few newborns. In our series, seven newborns whose maternal titers were RPR NR had RPR-positive cord serum samples. However, additional newborn serum testing only confirmed RPR positivity in one of the four newborns who were retested. It is possible that some of these mothers had false-negative results due to the prozone phenomenon, although we were unable to test this hypothesis since further testing on maternal serum could not be performed. The prozone phenomenon is a false-negative nontreponemal serologic test that can occur when undiluted serum containing high antibody titers is tested. Diluting the specimen solves this problem. The prozone phenomenon has been responsible for misdiagnosis of syphilis in pregnant women,¹¹ and clinicians should be

Table 3.—Newborns With Cord Serum Titer Four Times Their Mothers'*

Patient No.	Titer			Symptoms of Syphilis	Roentgenograms	CSF VDRL
	Cord	Newborn	Maternal			
1	1:4	1:2	1:1	—	ND	ND
2	1:8	ND	1:2	—	ND	ND
3	1:512	ND	1:32	—	ND	—
4†,‡	1:1024	ND	1:128	+	ND	ND
5†	1:1024	1:1024	1:256	—	+	+
6†	1:2048	ND	1:256	+	+	+
7†	1:2048	ND	1:64	+	+	+

*CSF indicates cerebrospinal fluid; ND, not done; minus sign, negative or normal; and plus sign, positive or abnormal.

†Newborns with congenital syphilis.

‡Patient died.

aware that many laboratories do not routinely dilute serum specimens for screening purposes.

Although maternal serology is superior to cord or newborn serum serology, it still may be of benefit to send both maternal and newborn specimens for analysis at delivery. This would provide a fail-safe mechanism in case the maternal specimen is not tested or the mother's specimen was negative due to the prozone phenomenon. This approach has been effective at Kings County Hospital.

Comparison of cord serologic results with newborn serum serologic results yielded more false-positive cord serologic results (10%) than false-negative cord serologic (5%) results. However, the correlation between cord and newborn serum samples results was very good when both specimens were RPR positive, with 91% of the cord and newborn serum samples being within two tube dilutions of one another. The problems with false-positive and false-negative cord results emphasize that the diagnosis of congenital syphilis should not rely on testing of the newborn, but on testing of the mother. Regardless of whether a newborn has positive or NR serologic results, if the mother has syphilis and needs treatment, the newborn needs treatment as well.¹² Since these data suggest that newborn serum testing is not clearly better than cord serum testing, it seems prudent to perform RPR testing on cord rather than newborn serum since it is easier to collect cord blood samples. Additional newborn specimens can be sent in individual cases for clarification of titers as necessary. A newborn should not be discharged from the nursery before the results of the maternal serologic test are available.⁵

Published reports are consistent with the finding that newborns with congenital syphilis can have NR nontreponemal antibodies at birth. In 1933, Roberts¹³ found that 37% of a group of 273 newborns with congenital syphilis had an NR Wassermann reaction on cord blood. Mascola et al,¹⁴ investigating 50 newborns with congenital syphilis, found five of 50 newborns had NR serologic findings at birth. More recently, Cohen¹² described seven of 154 newborns with congenital syphilis whose mothers were RPR positive and in whom cord blood was NR. Most newborns with congenital syphilis and NR cord RPRs will have mothers with positive serologic results and so will be identified if maternal screening is performed.

There will always be some newborns and mothers who are so recently infected that they both have NR tests at delivery. In a series of 22 mothers who were delivered of

newborns with congenital syphilis, Taber and Huber³ had six mother-newborn pairs with NR nontreponemal serologic results on both members of the pair. Similarly, Dorfman and Glaser¹⁵ had four mother-newborn pairs in their series who had both NR maternal and cord serology at delivery. The newborns later became symptomatic with congenital syphilis. No serum screening test will identify these mother-newborn pairs.

Our data confirm the belief that a newborn's titer that is fourfold higher than the maternal titer at delivery may be useful in making the diagnosis of congenital syphilis. However, this ratio is not absolutely diagnostic of congenital syphilis. Although this ratio is included in reviews¹⁶ and has been used as a diagnostic criterion for congenital syphilis,⁵ there are few data to support its use in the diagnosis of congenital syphilis. Taber and Huber³ found two of 45 newborns in their series with titers that were fourfold higher than their mothers'. Only one of these newborns had congenital syphilis. Mascola et al¹⁴ had three of 50 newborns with congenital syphilis who had cord titers fourfold higher than their mothers'. Similarly, Srinivasan et al¹⁷ found that only one of eight newborns with congenital syphilis had a titer fourfold higher than the mother's at birth.¹⁷ Our data indicate that it is not a sensitive or predictive test. Only four of the seven newborns with titers fourfold higher than their mothers' had obvious congenital syphilis. However, the three newborns without congenital syphilis did not have all possible tests performed, so the number with congenital syphilis could have been higher. The height of the titer may be more useful than the ratio of cord and maternal titers. All newborns with titers higher than 1:1024 had congenital syphilis, and all of them also had titers fourfold higher than maternal. The newborns with titers lower than 1:1024 and titers fourfold maternal did not have congenital syphilis.

Definitions of congenital syphilis have varied widely in the past few years.^{4,5,18} Congenital syphilis was strictly defined in this study to avoid overdiagnosis, and the number of newborns with congenital syphilis was probably higher than the 33 described herein. Use of *Tpallidum*-specific IgM Western blot¹⁹ and *Tpallidum* immunofluorescent antigen detection tests may provide better identification of infected newborns in the future.

A newborn serum specimen that is fourfold higher than maternal at delivery suggests congenital syphilis but should not be the only criterion used to make the diagnosis. Most newborns with this titer ratio had obvious

symptoms, and all had abnormal findings that enabled the diagnosis of congenital syphilis to be made without the use of this ratio.

Syphilis screening used at delivery should identify the largest number of infected mothers and their newborns. Cord screening is inadequate in that one third of infants and mothers will be missed. Using both maternal and newborn screening at delivery is the best way to identify infected mothers and newborns. Newborn cord and additional newborn serum specimens both have problems with false-positive and false-negative results, but cord blood is easier to obtain and is therefore preferable.

This work was aided by clinical research grant 6-FY90-570 from The March of Dimes Birth Defects Foundation, White Plains, NY.

The authors thank Laurence Finberg, MD, and William McCormack, MD, for their helpful comments in the production of this manuscript.

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How Are Pediatric Training Programs Preparing Residents for Practice?

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• The majority of pediatric residents continue to choose a career in practice on completion of their training. Despite knowing residents' career preferences, many training programs have focused on inpatient tertiary care at the expense of primary care. Perhaps this reflects service needs and the significant technology and extensive information resulting in the growth of pediatric subspecialties. To determine the spectrum of didactic and clinical experiences pediatric training programs offer residents to prepare them for managing a practice, we conducted a survey of pediatric training program directors in 1988. Although the majority of residency programs have a practice management curriculum, the number of hours devoted to this area is minimal. In addition, a significant number of residents are not experiencing a community office rotation. This survey indicates the need to develop a practice management curriculum if trainees are to be prepared for choosing the right career and for being competitive in practice.

(AJDC. 1991;145:1389-1392)

Preparing pediatric residents for careers in primary care practice has not been a major emphasis in most medical training programs.^{1,2} During the 1960s and 1970s, residency training focused on inpatient tertiary and subspecialty care, with primary care almost exclusively addressed within the confines of medical centers that serve an urban, poor population. Residents received little exposure to community pediatric resources and personnel outside the hospital.

The changing face of pediatric practice from the 1980s through the 1990s has been shaped by increased competition for patients, government regulations, rising costs of inpatient care, and other forces such as managed care. These changes have resulted in new career opportunities in primary care for residents. Since the majority of residents who complete their training continue to choose a career in practice, many programs have recently recog-

nized the need to incorporate education about community practice into the curricula to prepare residents for this career path.

The purpose of this survey was to determine what pediatric training programs are doing to prepare residents to manage a practice more effectively. The need for a survey addressing this issue was based on three criteria: (1) practitioners believe that their training did not adequately prepare them for practice³; (2) the majority of pediatric residents are involved in general pediatrics after completing residency; and (3) residents need to be exposed to practice by means of didactic and practical experiences to make informed career choices.⁴

To determine what didactic and clinical experiences pediatric training programs offer residents to prepare them for managing a practice, a survey was conducted of all pediatric training program directors in 1988. Members of the Education Committee of the Ambulatory Pediatric Association and representatives from the American Academy of Pediatrics assisted in the development of the survey questionnaire, which was mailed in March and June 1988 to all approved pediatric training programs. The questionnaire requested detailed information on whether each program included a curriculum devoted to practice management, and solicited information on didactic and clinical experiences, the settings for training, and faculty who were included in the program. Statistical analyses were performed using either descriptive statistics or analysis of variance (ANOVA) F tests, Students *t* tests, and χ^2 tests, as appropriate, for either discontinuous or continuous and normally distributed variables. All tests for significance were two-tailed, and the criterion for significance was $\alpha = .05$.

Department Editors.—Hugh D. Allen, MD, Columbus, Ohio; Fredric Burg, MD, Philadelphia, Pa; Harold Levine, MPA, Galveston, Tex; Barbara Starfield, MD, Baltimore, Md; Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Accepted for publication July 5, 1991.

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Table 1.—Curriculum Hours in Practice Management*

Teaching Format	Resident Year	No. of Hours		
		Mean \pm SD	Median	Range
Didactic	PL-1 (n=78)	4.6 \pm 5.4	3.0	0-20
	PL-2 (n=79)	5.0 \pm 4.9	3.0	0-20
	PL-3 (n=92)	7.8 \pm 8.5	4.5	0-50
Clinical experience	PL-1 (n=49)	31.9 \pm 4.0	0.0	0-360
	PL-2 (n=63)	55.0 \pm 81.8	10.0	0-360
	PL-3 (n=72)	79.5 \pm 79.2	4.0	0-400

*n indicates number of programs; PL, pediatric level.

RESULTS

Of the 233 resident training program directors surveyed, 137 (59%) responded after two mailings; their responses are included in the data presented.

Program Information

Survey respondents represented pediatric residency programs that included pediatric departments of university hospitals (38%), children's hospitals (21%), university-affiliated community hospitals (29%), non-university-affiliated community hospitals (3%), the military (7%), and unspecified programs (2%). Residency program directors stated that 59% of graduates in the previous 5 years had entered pediatric practice, 25% selected academic medicine, 12% entered the military or the public health service, 2% opted for research, and 2% chose other miscellaneous fields. Of those graduates completing their residency program in June 1987, 45% chose direct entry into pediatric practice, 29% opted for a fellowship with intent to enter academic medicine, 10% opted for a fellowship with intent to enter practice, while the smallest attributed selections were in the fields of military or public health (12%). Four percent of respondents chose other fields.

Curriculum and Education Issues

Two thirds of the resident program directors stated that their curriculum specifically included experiences designed to prepare residents for entry into the practice setting. Content areas reportedly offered included career decisions; establishing, joining, or managing a practice; community involvement; continuing medical education; participation in professional organizations; professional interests; and personal life-style. For most of the content areas listed, there was a progressively increased involvement of residents during the 3-year training period.

Program directors were asked to delineate the number of curriculum hours devoted to practice management at each residency level and in which format these presentations were offered (Table 1). The opportunities for clinical experiences increased progressively with the residency level and represented the major emphasis of time in the curricula. The number of didactic hours was limited, but increased slightly as residents progressed through their pediatric training. At pediatric level 1 (PL-1), six programs assigned more than 100 hours of clinical experience as did 13 programs at pediatric level 2 (PL-2) and 25 programs at pediatric level 3 (PL-3), causing the distribution and mean values to be positively skewed.

The survey also determined who provided instruction and the mode of presentation (Table 2). Examination of the survey responses revealed that full-time and voluntary faculty provided most of the teaching, and business consultants and hospital administrators also provided didactic presentations.

When program directors were asked how they chose the teaching faculty for practice management programs, 14 (12.3%) of 114 stated that they accepted all full-time and community volunteers; 55 (48.2%) said that they evaluated each prospective volunteer; and 78 (68.4%) declared that they recruited specific faculty. Some program directors used more than one approach.

A majority of the management programs offered experiences in community practice settings; in fact, 116 programs included elective (55%) or mandatory (38%) practice experiences in their curricula. Eight programs (7%) offered both elective and mandatory office experiences. In those in which the opportunity was elective, a mean of 2.8%, 17.5%, and 26.2% of PL-1s, PL-2s, and PL-3s, respectively, chose this option as part of their residency program.

The average length of time a resident spent in a community practice varied with the level of training (Table 3). Opportunities for this experience increased with training level and were most available to PL-2s and PL-3s ($P = .0001$). The most frequently reported amount of time available to these residents was a range of 1 to 4 weeks in an office setting.

Programs offered community office rotations to residents in a variety of practice settings: group practices, health maintenance organizations, health departments, school health programs, solo practices, and the military. Group and solo practices were predictably most frequently used, but health departments played a surprisingly large role, as did health maintenance organizations.

Seventy-four percent of the faculty members were generally informed of the curricular objectives, that is, what to teach. The day-to-day expectations and responsibilities of the resident in the practice setting included accompanying the practitioner on hospital rounds (67.8%), observing only (8.5%), observing and providing patient care (86.4%), and only providing patient care (6%).

Ninety-one percent of the programs required preceptors to complete written evaluations of each resident's performance, but only 69% required written evaluations of the experience and of the preceptor by the resident. Of those having measured responses, the program directors believed that the majority of both residents and preceptors considered the experience very good to excellent. Training program directors noted the major strengths of the office rotation were faculty commitment and resources, clinical setting, practical experience, curriculum, and resident-faculty relationship. Faculty commitment and resources, in addition to the physical setting of the experience, were rated the top two strengths.

Separate ANOVA F tests with post hoc comparisons were used to compare either hours of didactic or clinical experience assigned to pediatric level residents across different program types. A statistically significant different number of hours was noted for PL-1s across practice settings ($P = .0178$). Post hoc comparisons indicated that the number of didactic hours offered to PL-1 residents was similar among university-affiliated community hospitals, children's hospitals, and pediatric departments in university hospitals; however, the number of didactic hours was

Table 2.—Faculty, Format, and Time Spent in Practice Management Curriculum

Faculty	Total Time Spent, %			Teaching Format, (%)
	Mean \pm SD	Median	Range	
Practice management consultants	11.4 \pm 23.9	0	0-100	Didactic (100)
Business consultants	8.0 \pm 20.0	0	0-100	Didactic (100)
Full-time faculty	37.8 \pm 33.2	30	0-100	Didactic (65); practice (25); both (10)
Voluntary	38.0 \pm 32.3	40	0-100	Didactic (48); practice (25); both (27)
Hospital administration	4.7 \pm 9.8	0	0-50	Didactic (100)

Table 3.—Time Spent in an Office*

Resident Year†	Amount of Time, % of Residents				
	None	1 d	1-5 d	1-4 wk	>4 wk
PL-1 (n=84)	65	6	4	13	12
PL-2 (n=104)	38	4	10	29	19
PL-3 (n=121)	12	2	7	57	22

* $P = .0001$; $\chi^2 = 78.167$.

†PL indicates pediatric level.

Table 4.—Percentage of Office Experience Hours in the Pediatric Level 1 (n=48)

Institutional Setting	Amount of Time, % of Residents			
	None	1-3 h	4-8 h	>8 h
Children's hospitals (n=8)	100	0	0	0
Pediatric departments (n=21)	62	0	19	19
Military (n=6)	33	0	0	67
Community hospital, university-affiliated (n=13)	61	8	0	31
Community hospital, non-university-affiliated (n=0)	0	0	0	0

Table 5.—Time Spent in Elective and Mandatory Office Experiences by Pediatric Level (PL)

Resident Year	Amount of Time, No. of Residents		P	χ^2
	<1 month	>1 month		
PL-1 (n=67)				
Elective	38	1	<.01	9.480
Mandatory	20	8		
PL-2 (n=84)				
Elective	43	5	<.01	6.693
Mandatory	24	12		
PL-3 (n=98)				
Elective	57	5	<.001	17.903
Mandatory	20	16		

significantly higher for military residency programs. No statistical differences were found among the types of residency programs and number of didactic hours for PL-2 and PL-3 residents. Similarly, no statistical differences were noted for the number of clinical hours offered among the types of residency programs for PL-1 and PL-2 residents. Although based on the report of only 48 hospitals, pediatric departments, military, and university-affiliated community hospital programs were more likely to involve

PL-1s in a limited office experience than residency programs at children's hospitals. Table 4 shows categorical summaries of the reported hours. For PL-3 residents, there was a significant difference in the number of hours offered between military training programs and university-affiliated or children's hospital programs, with the number of clinical hours offered for PL-3s in military programs being significantly higher ($P = .0459$).

Results of the t tests showed that differences in the number of full-time or general/ambulatory pediatric faculty were not statistically significantly different between those programs that did and those programs that did not prepare residents for practice. Similarly, time spent in an office setting did not differ significantly between these groups. The number of residents in a training program also did not differ between programs with and without a practice management or office experience curriculum. Results of a χ^2 analysis indicated no statistically significant relationship between whether a program offered a curriculum and included time in an office setting. A significant ($P = .0103$) relationship exists between program curriculum type and office experience (elective or mandatory), with those programs without specific practice curricula more likely offering outside experience as an elective rather than a mandatory part of the program. In programs in which residents spent less time (<1 month) in offices, there was more likely to be an elective experience with each of the pediatric resident levels (PL-1, $P = .0021$; PL-2, $P = .0097$; and PL-3, $P = .0001$). For all pediatric residents, rotations of more than a month were more likely to be mandatory (Table 5). The requirement for preceptor evaluations was no more likely to occur in elective office rotations than in mandatory office rotations; however, residents' evaluations were more likely to be required for mandatory programs ($\chi^2 = 4.4$; $P = .0360$). No statistical relationship existed between the residents' and preceptors' evaluations of the rotation and the amount of time spent in an office setting as reported by resident training directors. The reported evaluations of the preceptors and residents were highly statistically correlated ($r = .78$, $P < .001$).

COMMENT

The practice of pediatrics has undergone major transformation. As an example, infants with failure to thrive may have been routinely hospitalized in the past, but now are often assessed and treated as outpatients. Diagnosis-related groups have mandated shorter hospital stays, changed reimbursement procedures, and shifted care to the home, clinics, health departments, and private pediatric offices. Other influencing variables include uncompensated care, the focus on tertiary care, high operational costs in medical centers, and competition among trainees for patients in university-based programs. These forces, among others, have stimulated the academic community to reexamine how care and training have traditionally

been offered and to open new partnerships with resources in the community.

Program directors confirmed that in the previous 5 years, a majority of their graduates continued to enter practice. Finding that two thirds of the resident program directors have curricula that specifically address preparing a resident for practice was more than was anticipated. We postulated that those programs with a practice management curriculum would have a larger number of residents in the program, but this assumption was not supported statistically. While the number of residents in a program is not a critical factor, scheduling, enlisting faculty, and agreeing on core curriculum are key variables that must be considered in the development of this curriculum.

The major responsibility for teaching the curriculum is assumed by full-time and voluntary faculty, but programs do involve nonmedical personnel in teaching didactic issues as they pertain to practice. Although it was hypothesized that those departments with large numbers of general/ambulatory faculty would more likely have curricula addressing practice management, this was not the case for either didactic or practice experiences. The incorporation of this program into the curriculum may be more dependent on an individual or core group of faculty who assume leadership and advisory roles in this area.

Our data confirm that a greater emphasis is given to practice management in the military than in other training programs. This focus perhaps reflects requirements of military residents on their completion of training, ie, that they administer and provide care in a military health care facility. The military health system is structured and consistent across different service branches and resembles a pre-paid health maintenance organization. In this setting, there is no need for residents to spend time in private offices because their needs are met from within the program.

Not unexpectedly, the survey documents that a number of residency programs still do not offer any experience to residents in an office setting outside the medical center. This is in spite of the fact that in the American Medical Association's *Directory of Graduate Medical Education Programs*, the section on pediatrics states that certain aspects of ambulatory care deserve special attention, such as office electives or preceptorships, and the implementation of such experiences would be an important consideration in the accreditation review.⁵ Thirty-nine percent of programs do not include an office rotation for PL-2s and it is precisely at this level that residents are trying to make informed career decisions. More programs are involved in the office concept as the PL-3 year is approached, but this timing can create confusion for residents when there are pressures to make an earlier career decision, such as committing to a fellowship in their second year of training.

Those programs with formal curricula tend to offer more didactic information during the PL-1 year than other levels of training and an increasing amount of practical experience, with progression through the PL-2 and PL-3 years. However, on average, the actual number of curricular hours offered at each resident level of training is minimal, at best, with median values even lower. Two major factors were related to whether an office experience was mandatory or elective: the presence of a curriculum, and the resident spending 1 month or more in an office.

Both of these factors demonstrate a commitment on the part of the training program to this concept.

The variety of practice settings used by residency programs is impressive, from traditional solo or group practices to health departments and health maintenance organizations. As the practice of medicine becomes more complex and the delivery of health care changes, residents will need to observe these differences first-hand to make their career plans and consider their career options. Examining their priorities and seeing how these best fit with what is available in practice options are more likely to result in career satisfaction.

Although there may be some sampling bias in that we did not follow up with nonresponders, this survey documents that the majority of residency training programs have at least some curricula to prepare residents to enter pediatric practice. The problem is that the number of hours devoted to practice management is generally minimal, considering the number of trainees who choose practice for their career. In addition, a significant number of residents are not experiencing a community office rotation, which when offered in the curriculum, is rated highly. Participation in the office setting can assist residents in determining if practice is the most desirable career path. Finally, this study indicates the need to develop a meaningful curriculum in practice management if graduates of residency programs in the 1990s are going to be prepared for and competitive in pediatric practice. For those programs planning to implement a practice management curriculum, a number of models have been described.⁶⁻¹¹ Reaching a consensus on a core curriculum in this area from organizations such as the Ambulatory Pediatric Association, American Academy of Pediatrics, and the Association of Medical School Pediatric Department Chairmen would be an important contribution.

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Breathing Patterns and Heart Rates at Ages 6 Weeks and 2 Years

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● Forty-two randomly selected, full-term, healthy infants underwent 24-hour electrocardiographic recordings and breathing movements at about ages 6 weeks (median age, 43 days; range, 34 to 61 days) and 2 years (median age, 26 months; range, 21 to 35 months). The number and duration of apneic pauses of 3.6 seconds or longer were analyzed. Periodic apnea was defined as a sequence of three or more apneic pauses, each separated by fewer than 20 breaths. All other apneic pauses were defined as isolated. Median heart rates and respiratory rates, which were measured during regular breathing, decreased from 137/min and 35/min to 98/min and 21/min, respectively. The total duration of periodic apnea remained unchanged (median, 0.06 min/h vs 0.05 min/h). Although the median frequency of all isolated apneic pauses decreased from 3.6/h to 2.5/h, the number of those that were longer than 6 seconds increased from 0.37/h to 0.80/h, leading to an increase in the proportion of these pauses, among all isolated apneic pauses, from 10% at age 6 weeks to 32% at age 2 years. Only one apneic pause in one infant at age 6 weeks, but eight pauses in six children at age 2 years, were longer than 15 seconds. A knowledge of such normal variability in the duration of apneic pauses in older infants and young children is essential for the interpretation of pneumograms and alarms while monitoring breathing movements.

(AJDC. 1991;145:1393-1396)

Many studies have analyzed heart rates and breathing patterns in infancy¹⁻⁵ and found that the frequency of apneic pauses during the first 6 months of life decreases with age. It has been suggested that this decrease indicates a maturational process in the respiratory center of the brain stem. Data to follow this process into childhood have not been available.

Long-term recordings of respiration and heart rate (pneumograms) are used to identify an abnormal regulation of breathing in infants who are considered at risk of sudden death. Based on normative data obtained in full-

term infants in their first 6 months of life, the finding of prolonged apneic pauses in these recordings is widely considered to indicate a potentially dangerous abnormality in the regulation of respiration.⁶⁻⁸ The definition of prolonged apneic pauses varies. While many authors follow that of the American Academy of Pediatrics, which defined a prolonged apneic pause as a cessation in breathing movements of 20 seconds or longer,⁸ others regard any apneic pause longer than 15 seconds as prolonged.^{6,9,10} As a result, an alarm threshold of 10 to 20 seconds is used in most home monitors, which detect an absence of breathing movements.¹¹⁻¹³

Prospective population-based studies, however, have failed to show that prolonged apneic pauses are more frequent in infants who subsequently die of sudden infant death syndrome.¹⁴ Moreover, there is little knowledge about normal breathing patterns beyond the first 6 months of life. In this study, 24-hour electrocardiographic recordings and abdominal wall movements were performed sequentially in 42 healthy, full-term infants at about ages 6 weeks and 2 years.

SUBJECTS AND METHODS

Forty-two full-term subjects were selected at random from a population-based sample who had undergone an initial recording at about age 6 weeks as part of a prospective study of sudden infant death syndrome.¹⁴ For the purpose of this study, parental consent was given to an additional recording in this subgroup at age 2 years. Parents were reassured that the aim of the study was the acquisition of normal data, and that the recording would not interfere with the normal care of their child. Of the 42 children studied, 22 were male. Their birth weights ranged from 2500 g to 4560 g (median, 3350 g), and gestational age at birth from 38 weeks to 42 weeks (median, 40 weeks).

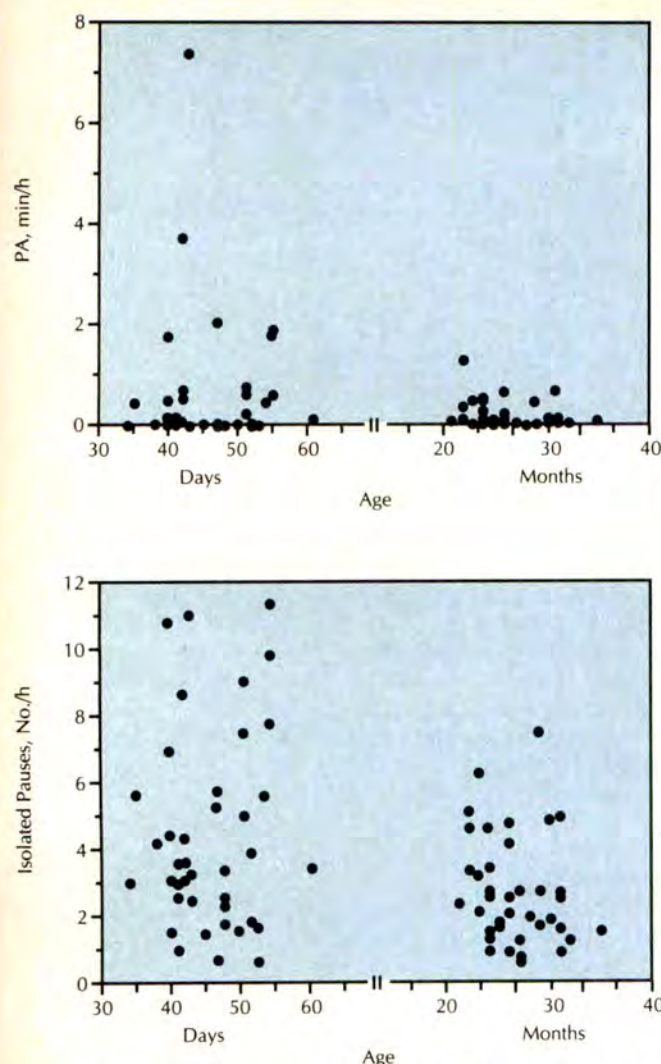
Recordings were performed in the children's homes between 34 days and 61 days (median, 43 days) and between ages 21 months and 35 months (median, 26 months). Recordings were performed only if the child was in good health, that is, free of major symptoms or disease. At the time of the 6-week recording, three infants were reported to have colic, and four were reported to have a cold (cough and/or sniffles). At the time of the second recording, 10 children were reported to have a cold.

All subjects underwent 24-hour recordings of their heart rates (from a modified lead I configuration) and breathing movements (Graseby pressure capsule). These signals were recorded on a portable cassette recorder (Medilog 1, Oxford Medical Systems, Oxford, England). The recordings were set up by a research worker and terminated by the parents about

Accepted for publication June 10, 1991.

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Duration of periodic apnea (PA) in minutes per hour of recording (top), and number of isolated apneic pauses of 3.6 seconds or longer per hour of recording (bottom), related to age at the time of the recording. Note the different units on the x axis.

24 hours later. The ability of the pressure capsule transducer to provide accurate information on breathing patterns has been verified by comparison with simultaneous recordings using impedance pneumography, respiratory inductance, and jacket plethysmography.¹⁵

The recordings were replayed with an ink jet chart recorder (Mingograf 34T, Siemens-Elema, Stockholm, Sweden) at a speed of 1.2 s/mm. Printouts were analyzed by three workers who were blind to the source of the data. Periods of regular and nonregular breathing patterns were defined as described previously.⁵ In summary, regular breathing is a reproducible pattern in which breathing movements are steady in rate and amplitude. Periods not conforming to this definition were classified as nonregular. Heart and respiratory rates were analyzed at the middle of each period of regular breathing for 6 seconds and 1 minute, respectively, at least 10 seconds away from apneic pauses or sighs, and averaged for the whole recording. Pauses in breathing movements of 3.6 seconds or longer were counted and their durations measured. These apneic pauses were grouped according to their duration, that is, 3.6 seconds to 6 seconds, 6.1 seconds to 12 seconds, or greater than 12 seconds. Periodic apnea was defined as a sequence of three or more apneic pauses, with each pause separated by fewer than 20 breaths.⁵ All apneic pauses appearing out of such sequences were regarded as isolated. The term periodic apnea was chosen rather than periodic breathing, as the latter in-

Comparison of Variables Measured at Ages 6 Weeks and 2 Years*

Variable	Median (Range)		P
	6 wk	2 y	
Respiratory rate, breaths/min	35 (23-51)	21 (15-31)	<.001
Heart rate, beats/min	137 (96-159)	98 (73-120)	<.001
Duration of PA, min/h	0.06 (0.0-7.4)	0.05 (0.0-1.3)	NS
No. of pauses in PA/h	0.2 (0.0-23.9)	0.2 (0.0-3.8)	NS
% of pauses in PA 3.6 - 6.0 s	85 (40-100)	77 (50-100)	NS
% of pauses in PA 6.1 - 12.0 s	13 (0-60)	19 (0-50)	NS
% of pauses in PA >12.0 s	0 (0-3)	0 (0-25)	NS
No. of isolated pauses per hour	3.6 (0.7-11.5)	2.5 (0.6-7.5)	<.01
% of isolated pauses 3.6 - 6.0 s	89 (64-100)	65 (37-90)	<.001
% of isolated pauses 6.1 - 12.0 s	10 (0-36)	32 (10-57)	<.001
% of isolated pauses >12 s	0 (0-3)	0 (0-13)	<.001
Duration of longest pause overall, s	9.0 (6.0-18.0)	12.6 (7.2-19.2)	<.001

*P values were obtained using the Wilcoxon Signed Rank Test; PA indicates periodic apnea, and NS, not significant.

cludes recurrent episodes of hypoventilation,⁵ which were not included in this analysis.

Results are presented as means and SDs or medians and ranges for each variable, with frequencies per hour of recording. Comparisons between values obtained at ages 6 weeks and 2 years were performed using Wilcoxon's Signed Rank Test. Correlations were assessed using Spearman's rank correlation coefficient.

RESULTS

The mean duration of the initial recording was 22.4 hours (SD, 1.1 hour), and of the second recording, 21.0 hours (SD, 2.3 hours). The mean duration of regular breathing was 3.7 hours (SD, 0.9 hour) at about age 6 weeks, and 3.3 hours (SD, 1.8 hours) at age 2 years. The initial and follow-up recordings did not show a significant difference in any of the variables studied between subjects with and without a cold ($P > .05$, Mann-Whitney *U* test). There was also no evidence that, within the range of ages at each recording, age affected the results (Figure). Therefore, results for both the initial and follow-up recordings are presented without regard to age or the presence of a cold, and are summarized in the Table.

Heart and respiratory rates were significantly lower at age 2 years. Every recording contained apneic pauses. In their initial recordings, 29 infants (69%) showed periodic apnea; this proportion remained almost constant, with 67% of the recordings (28) obtained at age 2 years containing such episodes. Neither the number of pauses during periodic apnea nor the proportion of time spent in this pattern changed significantly. However, at age 6 weeks, there was a small number of infants with extremely long-summed durations of periodic apnea. By age 2 years, most of these extreme values were not seen (Fig-

ure). The proportion of periodic apneic pauses longer than 6 seconds was higher at age 2 years than at age 6 weeks; however, these differences were not significant.

The frequency of isolated apneic pauses was significantly lower at about age 2 years ($P < .01$). Again, this distribution was more skewed at age 6 weeks than at age 2 years (Figure). In contrast, the mean duration of these pauses was longer, as expressed by the increase in the proportion of isolated apneic pauses with durations of more than 6 seconds. Thus, the overall trend in the frequency of isolated apneic pauses to decrease was reversed for the group of pauses of 6.1 seconds to 12 seconds, whose median frequency more than doubled from 0.37/h at age 6 weeks to 0.80/h at age 2 years ($P < .02$). Moreover, the median duration of the longest apneic pause (isolated or periodic) observed in each recording was significantly longer at age 2 years than at age 6 weeks ($P < .001$). In the initial recording, one infant exhibited an apneic pause longer than 15 seconds. In the second recording, six children had a total of eight pauses of greater than 15 seconds in duration.

The frequency of isolated apneic pauses was directly proportional to that of periodic apneic pauses in both the initial and follow-up recordings ($r = .91$ and $.80$, respectively; $P < .0001$). Thus, at both ages, the subjects with high numbers of isolated apneic pauses also showed more periodic apnea. There was also a significant correlation between individual values at the initial and follow-up recordings for the number of pauses in periodic apnea ($r = .37$, $P < .02$), but not for heart or respiratory rates ($r = .20$ and $.12$, respectively; $P > .05$), or isolated apneic pauses ($r = .26$, $P = .09$).

COMMENT

This study highlights some of the changes that occur in respiratory patterns between early infancy and early childhood. However, our data address only respiratory rates and pauses in abdominal wall movements. The recording technique used cannot detect such phenomena as obstructive, mixed, or expiratory apnea. Our findings at about age 6 weeks are comparable with those in other studies¹⁻⁵ that show a nonnormal distribution of apneic pause frequency and duration of periodic apnea with a wide scattering of values (Figure). However, comparability of absolute figures for apneic pause frequency with those of other studies is limited due to different definitions of apneic pauses. Data concerning respiratory patterns at age 2 years are not available to compare with our findings. Our data remain statistically significant even when adjustment is made for the increased probability of a false-positive result due to multiple tests of significance. Even after making the most conservative adjustments to the P values (Bonferroni adjustment), all of the results remain highly significant ($P < .01$).

The proportion of children exhibiting periodic apnea and the median duration of this pattern remained almost constant between the two ages. However, there was a much narrower range in the duration of periodic apnea at age 2 years (Figure). During the first 6 months of life, Carse et al¹ included pauses of 2 seconds or longer in their analysis and found a significant decrease in periodic apnea. In contrast, the study by Richards et al⁵ showed that the duration of periodic apnea decreased significantly only between the first and sixth week of life, and remained constant thereafter, whereas Hoppenbrouwers

et al³ analyzed pauses of 3 seconds to 6 seconds and found stable values for periodic apnea during the entire first 6 months of life. From the data in this study, it may be speculated that in the majority of the children, the proportion of time spent in periodic apnea did not change substantially between the second month and the second year of life.

The decreasing number of isolated apneic pauses with age corresponds with results of developmental studies of apneic pause frequency during infancy.¹⁻³ However, both the proportion of apneic pauses of more than 6 seconds and their absolute number, as well as the duration of the longest apneic pause, were higher at age 2 years than at age 6 weeks. Moreover, apneic pauses longer than 15 seconds, a duration widely considered as abnormal in infancy^{6,9,10} and rare in our own group when studied initially, appeared more frequently in the older age group. A tendency for apneic pauses of more than 6 seconds to increase in frequency during the second half of the first 6 months of life, associated with a decreasing frequency of shorter pauses, has been described by Richards et al.⁵ These authors also found a positive correlation between age and increasing duration of the longest pause beyond the first month of life.

The present data cannot be used to explain why the duration of apneic pauses increases with age. This increase may be related to the decrease in the respiratory rate, which, together with the activity of lung reflexes, such as the Hering-Breuer lung inflation reflex,¹⁶ may result in longer pauses since the average number of "missed breaths" during an apneic pause remains constant. However, these speculations require further investigation.

Clinically, the finding of pauses of up to 19 seconds in healthy infants is important in relation to the interpretation of pneumograms performed in this age group. Parental reports of alarms occurring on breathing movement detectors used for home monitoring in young children should also be interpreted with caution. As mentioned above, most monitors alarm after breathing movements have not been sensed for 10 seconds to 20 seconds (this interval being derived from studies on young infants). A proportion of infants at risk of sudden death are monitored beyond their first year of life, and the retention of an alarm setting for a 20-second apneic pause will result in alarms from normal respiratory phenomena. Further support for the latter has been given by data from a recent study by Weese-Mayer et al,¹⁷ who performed event recordings of heart rate and breathing movements in infants and children at risk of sudden infant death syndrome. They found an increase in the number of apneic pauses longer than 15 seconds with increasing age, with apneic pauses of 25 seconds or longer becoming a frequent event in children older than age 5 years.

These results suggest that the common definition of an "abnormal" apneic pause duration is too simplistic since it does not account for age. From a physiologic viewpoint, the effect of an apneic pause on blood gas homeostasis must be more important than the duration of the pause. Therefore, future studies on respiratory pathophysiology in infants and young children should include continuous measurements of oxygenation. This approach may provide more direct information about potentially dangerous respiratory pathophysiology.

Dr Poets' research was funded by Deutsche Forschungsgemeinschaft, Bonn, Germany; Mrs Valerie Stebbens by the Nuffield Foundation, London, England; and Dr Southall's by the Royal Brompton National Heart & Lung Hospitals, London, England; and Nellcor Inc, Hayward, Calif.

The authors gratefully acknowledge the support of the British Heart Foundation, London, England; the Foundation for the Study of Infant Deaths, London, England; and the people of Doncaster and Brighton, England, for their support of data collection; Vivian G. Taylor for data management; and Jackie Kelly, Pauline Mills, and Wendy Yates for data analysis.

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Pictures From the Heart

A 7-year-old hemophiliac boy with acquired immunodeficiency syndrome asked his mother why a young friend had recently died. She replied, "You never have to lose somebody you really love. You can keep them with you always in your heart." She continued, "Did you know your heart can take pictures, and they are the best kind because you can take them at the most special moments, and nobody has those same pictures but you."

Oyler C. *Go Toward the Light.* New York, NY: New American Library; 1990:58-59.

Cardiac Care for Infants

Determinants of Hospital Charges for Acute Care

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• We analyzed hospital use and inpatient charges retrospectively for infants hospitalized at a tertiary referral center in the first year of life for cardiac disease. For 93 infants hospitalized between August 1987 and June 1989, there were 1.8 admissions per patient, with a median stay of 14 days; 24.7% required more than 28 days of acute inpatient care. Total hospital charges (excluding professional fees) in the first year of life were \$34 176 12, which represents \$36 749 per infant and \$35 386 per survivor. Reimbursement totaled 93.2% of charges. Multivariate analysis revealed that complex disease, surgery, and length of stay in the intensive care unit were significantly associated with increased charges, while extracardiac anomalies, birth weight, outcome, and type of insurance were not. The economic benefits of averting infant death outweigh the associated costs by as much as 5.4 to 1. We conclude that current treatment of most infants with cardiac disease is both effective and economically beneficial.

(AJDC. 1991;145:1397-1400)

Changes in the management of cardiac disease in infancy during the past 20 years have resulted in a majority of definitive surgical procedures being performed before a child's first birthday^{1,2} and thus a concomitant reduction in subsequent operations and hospitalizations. This change has implications for the pattern of expenditures for pediatric cardiac disease in infants. In recent years, attention has been drawn repeatedly to the issues of cost and access to medical care and, more recently, to the question of access to care for children with cardiac disease.³ It is valuable, therefore, to determine the magnitude of hospital expenditures for infants younger than 1 year with cardiac disease, which in turn allows estimation of the relationship between costs and benefits associated with infant cardiac disease. To do this, we analyzed hospital use and inpatient charges at a tertiary re-

ferred center for infants hospitalized for cardiac disease in the first year of life, and we report our findings herein.

PATIENTS AND METHODS

The present study is part of a larger investigation of determinants of outcome in hospitalized infants with heart disease.⁴ Infants admitted to The Johns Hopkins Hospital Children's Center, Baltimore, Md, in 1988 with cardiac disease were identified retrospectively. Information concerning other admissions between birth and 1 year of age was obtained for these infants, thus generating a complete record of inpatient care during the first year of life, which spanned the period from August 1987 through June 1989 for this cohort. Preterm infants with isolated persistent ductus arteriosus were excluded. Only those infants who received all care in the first year of life at The Johns Hopkins Hospital were included, so that data on charges would be comparable for the cohort.

The following patient data were obtained: race, sex, birth weight, source of medical insurance, charges for inpatient care, type of surgery if applicable, number of admissions, total number of days in the hospital and intensive care unit during the first year of life, cardiac diagnoses, extracardiac defect(s), and outcome at 1 year of age. Cardiac disease was classified as complex or noncomplex⁴ based on a spectrum of severity. Complex defects comprised those in which there were not two adequately functioning ventricles, including hypoplastic left- and right-heart syndromes, septal malalignment, outflow atresia, and cardiomyopathy. Extracardiac anomalies included chromosomal abnormalities, mendelian and other syndromes, and other major anomalies. Charges for inpatient care for each patient (excluding professional fees), as well as source and amount of reimbursement, were obtained from The Johns Hopkins Hospital Billing Department.

Statistical analysis was performed with the Mann-Whitney *U* test, coefficient of determination, and multivariate techniques. A multiple linear regression model was constructed to examine the effect of each independent variable on total charges, while holding the remaining covariates constant. The following independent variables were entered into the regression equation: complexity of the lesion, presence of extracardiac anomalies, surgery, birth weight, type of insurance, length of stay in the intensive care unit, and 1-year outcome. Length of hospital stay was not included in the model because of the high degree of correlation between this variable and length of stay in the intensive care unit. All tests of significance were two-tailed and were based on rejecting the null hypothesis at the *P* = .05 level.

Approval for the project was granted by the Joint Committee on Clinical Investigation of The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital, Baltimore.

Accepted for publication June 24, 1991.

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Presented in part at the Mid-Atlantic Pediatric Cardiology Society Meeting, Bethesda, Md, May 17, 1991.

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Table 1.—Characteristics of Study Patients (N=93)

Characteristic	No. (%) of Patients
Complex disease	31 (33.3)
Extracardiac anomaly	29 (31.2)
Both complex disease and extracardiac anomaly	10 (10.8)
1-y mortality	24 (25.8)
Surgery	
Patients	66 (71.0)
Procedures	88 (94.6)

RESULTS

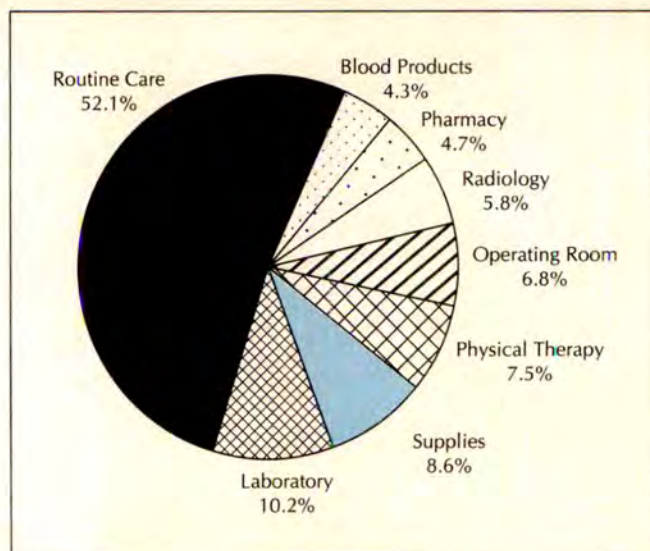
Complete data were available for a total of 93 patients who met the study criteria. Characteristics of these infants are presented in Table 1. As shown, 31 patients (33.3%) had complex cardiac disease, 29 (31.2%) had one or more extracardiac anomalies, and 10 (10.8%) had both complex disease and extracardiac anomalies. The infant mortality rate in the total cohort was 25.8% (24/93). A total of 66 patients (71.0%) had undergone 88 surgical procedures, or 0.9 procedure per study patient and 1.3 procedures per patient who underwent surgery.

Hospital admissions totaled 167, or 1.8 per patient, with a median length of stay of 14 days (range, 1 to 241 days). Twenty-three infants (24.7%) required more than 28 days of acute inpatient care during the first year of life. Of the 2679 total hospital days, 1642 (61.3%) were spent in intensive care units.

Data concerning hospital charges are shown in the Figure. Total hospital charges (excluding professional fees) in the first year of life were \$3417612, which represents \$36749 per infant (range, \$1003 to \$306043). Hospital charges are separated by The Johns Hopkins Hospital into eight categories. Routine care charges (for basic room, board, and nursing) accounted for 52.1% of the total (\$1776188). The second largest component of total charges was laboratory charges (10.2%; \$350086); this component includes charges for respiratory care, such as ventilators and blood gas analyses. Other charges were for medical and surgical supplies (8.6%; \$294867), physical therapy (7.5%; \$255849), operating room time and supplies (6.8%; \$234345), radiologic procedures (5.8%; \$198921), pharmacy supplies (4.7%; \$160542), and blood and related products (4.3%; \$146814).

Table 2 presents information about the source and amount of reimbursement for these charges. The total amount of reimbursement, \$3185322, represents 93.2% of total charges, leaving 6.8% as unreimbursed care. Medical Assistance was the largest single third-party payer, with 36.7% of total reimbursement, followed by "other sources," which included commercial insurers and self-payment (35.5%) and Blue Cross (27.4%). CHAMPUS accounted for less than 1% of total reimbursement.

Mean charges for infants with complex cardiac disease were 53.2% higher than for infants with noncomplex disease (\$47820 vs \$31213), but this difference did not reach statistical significance (Mann-Whitney *U*, 810; *P* = .22). Similarly, mean charges for infants with extracardiac anomalies were 69.1% higher than for infants without such anomalies (\$51123 vs \$30235); this difference was statistically significant (Mann-Whitney *U*, 679; *P* = .04). If



Breakdown of hospital charges. Total hospital charges were \$3417612.

Table 2.—Source and Amount of Reimbursement

Source of Reimbursement	Amount, \$	% of Charges
Medical Assistance	1 168 059	34.2
Blue Cross	871 716	25.5
CHAMPUS	13 367	0.4
Other (commercial, self-pay)	1 132 180	33.1
Total Reimbursement	3 185 322	93.2

the mean charges for infants with neither complex cardiac disease nor extracardiac anomalies are compared with those for other study infants, even more striking differences emerge. Infants with neither complex disease nor anomalies had mean charges 61.1% lower than those for other infants (\$20345 vs \$53013; Mann-Whitney *U*, 682; *P* = .003).

For infants who died before age 1 year, mean charges were \$40664, compared with survivors for whom mean charges were \$35386, a 14.9% difference (Mann-Whitney *U*, 800; *P* = .8). Another, more conservative way to assess costs of care is to attribute all hospital charges incurred by the 93 study infants to be of the 69 survivors. When this is done, the mean charge per survivor is calculated to be \$49531.

Undergoing one or more surgical procedures significantly affected mean charges (\$46708 vs \$12402; Mann-Whitney *U*, 299; *P* < .0001). Length of hospital stay was highly correlated with charges ($r^2 = .9470$; *P* < .0001), as was length of stay in the intensive care unit ($r^2 = .9299$; *P* < .0001).

Results of the multiple linear regression analysis are shown in Table 3, which includes variable estimates for each independent variable, the *t* value for each variable estimate, and the *F* value and r^2 for the model. The *F* value indicates that the model as a whole is statistically significant (ie, significantly different in explanatory ability from having no model), and the r^2 value indicates that the independent variables together explain approximately 90% of the variance in the dependent variable, charges. As

Table 3.—Results of Multiple Linear Regression Analysis (Dependent Variable Is Hospital Charges) (F=117.54 and $r^2=.9006$)

Independent Variable	Variable Estimate	t for Null Hypothesis (Variable=0*)
Complex disease (1=yes)	+7531.36	2.062†
Surgery (1=yes)	+20,464.21	5.104‡
Days spent in intensive care unit	+1472.93	23.395‡
Extracardiac anomalies (1=yes)	-1751.47	-0.448
Outcome (1=yes)	-1260.53	-0.292
Birth weight, g	+2.46	0.950
Insurance (1=private)	-6371.15	-1.644

*† Test value when testing the null hypothesis that the variable does not differ significantly from zero.

† $P<.05$.

‡ $P<.0001$.

shown, complex disease was significantly associated with increased charges in this model, but extracardiac anomalies were not, in contrast to the univariate results. Surgery and length of stay in the intensive care unit also were significantly associated with increased charges, while the remaining variables showed no significant association.

COMMENT

In a population of infants with cardiac disease requiring hospitalization in the first year of life, we found that nearly 75% survived and that the mean first-year hospital expenditure (excluding professional fees) was \$36749 for all infants and \$35386 per survivor. Data regarding professional fees were difficult to obtain retrospectively and hence were not included in the formal analysis. Some information was available, however, for 60 of the 93 study infants, for whom hospital charges were \$2408939, estimated cardiology fees were \$150612, and estimated surgery fees were \$148050 (40 of the 60 underwent surgery). Thus, for infants undergoing surgery, the average professional fee was \$6200, representing an additional approximately 15% addition to the mean hospital charge. Data available for 58 of the 60 patients indicated that the average reimbursement rate for professional fees was approximately 47%, in sharp contrast to the rate for hospital charges. Future prospective studies should include more detailed analysis of professional fees charged and of reimbursement rates. It is evident that although physician fees are an important component of overall costs to the family and society, their omission from the present analysis would not bias the overall conclusions.

The benefit of saving a life often is quantified in terms of the economic benefit that individual can be expected to contribute to society during a productive lifetime. For children younger than 1 year, the present value of lifetime earnings has been conservatively estimated at \$191184 (based on means for men and women).⁵ Employing this figure, we estimate the economic benefits of averting death in infancy for the 69 survivors to be \$13191696 compared with total hospital expenditures of \$2441634,

yielding a benefit-to-cost ratio of 5.4 to 1. A number of caveats must be mentioned in interpreting this figure. First, the hospital expenditures are charges, not costs, although charges are likely to exceed costs, making our estimate conservative. Second, the expenditures include only those for acute care for survivors in the first year of life. Other costs for subsequent acute or chronic medical care are excluded, leading to possible underestimation of chronic medical care costs for infants with extracardiac anomalies, including Down's syndrome. Third, the value of the benefits assumes that all first-year survivors enjoy the productive life expectancy of the average worker. This view may be optimistic, but most recent survivors of cardiac operations performed during early infancy have normal or optimal cardiac health.⁶ Even if the medical care expenses are doubled and the estimated societal contribution is halved, however, the benefit-to-cost ratio remains greater than 1 (1.4 to 1). Furthermore, these calculations ignore the inestimable psychological benefit to the family of averting an infant death.

The magnitude of hospital charges reported herein is consistent with results from studies that have examined the costs and benefits of cardiac care^{6,7} as well as other technologically intensive medical interventions, such as neonatal intensive care^{8,9} and extracorporeal membrane oxygenation.¹⁰ In a study from the New England Regional Infant Cardiac Program concerning the cost of hospital care for infants with cardiac disease, Fyler¹¹ reported that the cost per patient younger than 1 year was estimated to be \$9000, and the cost per survivor was approximately \$18000 (in 1979 dollars). If Fyler's estimated costs are inflated to 1988 dollars,¹² the costs per patient and per survivor would be \$18480 and \$36954, respectively. Fyler's cost analysis, like ours, was based on hospital bills rendered. In our study, mean charges per patient were \$36749, considerably higher than Fyler's adjusted costs. This discrepancy can be explained in large part by differences in surgical management of infants between the late 1970s and the present. In Fyler's population, there was 0.55 surgical procedure per patient younger than 1 year. In contrast, in our study, there was 0.9 surgical procedure per patient younger than 1 year, which reflects the trend toward earlier repair. In our multivariate model, undergoing surgery represented an increase in charges of \$20464, so that the difference in surgery alone could explain a substantial portion of the difference between Fyler's figures and those reported herein.

In contrast to the mean expenditure per patient, the mean expenditure per first-year survivor in our study (\$35386) is lower than the estimated cost (in 1988 dollars) per survivor in Fyler's cohort (\$36749). This almost certainly reflects the emerging paradigm for many newborns with serious heart disease, which is early, definitive surgical repair, followed by a relatively uncomplicated recovery. Moreover, the survivors in our cohort are likely to be infants with more complex lesions, so the lower contemporary expenditures are even more remarkable.

Results of our multivariate analysis emphasized the influence of complex disease, surgery, and length of stay in the intensive care unit on hospital charges. These factors are interrelated in that infants with complex disease are more likely to undergo multiple surgical procedures, and thus spend more days in the intensive care unit, but the regression analysis showed them each to be indepen-

dently associated with charges as well. From a health policy perspective, this analysis suggests that efforts to prevent the birth of infants with complex cardiac disease may result in reduced expenditures.

Our data concerning expenditures reflect only those infants who required hospitalization in the first year of life. Current practice patterns that emphasize outpatient management whenever possible, including outpatient cardiac catheterization, mean that many infants no longer require hospitalization for diagnosis and management. Thus, for example, infants born with small or moderate-sized ventricular septal defects, the most frequent cardiac lesion, are not represented in our study. If all infants with structural cardiac lesions were in the denominator in our study, the cost per cardiac infant would be reduced substantially.

The expenditure data presented herein represent charges incurred only in the first year of life. Given the pattern of early repair for correctable lesions, the majority of charges should occur in the first year of life, ideally with only routine follow-up subsequently. Of the 93 patients, only 11 (with complex disease) had not yet undergone a definitive surgical procedure by age 1 year. Nevertheless, estimates of the total hospital expenditures associated with cardiac disease in childhood require long-term follow-up of the cohort. Future analyses of professional fees and hospital charges for both acute and chronic care in the long term are warranted.

Congenital anomalies are the fifth-ranking cause of premature death in the United States, and cardiac malformations account for 44% of this burden.¹³ The cost to society of premature death is quantified by the concept of years of potential life lost, which represents lost economic productivity. In this context, although the cost per survivor may seem high, it is considerably lower than the estimated \$191 184 in lost productivity to society for each infant death. We conclude that the current approach of early definitive repair of cardiac defects in a major tertiary care center is beneficial in both therapeutic and economic terms. Further studies concerning long-term expendi-

tures are needed, particularly in infants with complex defects not amenable to one-stage repair, and concerning the long-term quality of life and productivity of surviving infants.

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Taurine Decreases Fecal Fatty Acid and Sterol Excretion in Cystic Fibrosis

A Randomized Double-blind Trial

Lesley J. Smith, MD; Florence Laçaille, MD; Guy Lepage, MSc; Nancy Ronco, RT;
André Lamarre, MD; Claude C. Roy, MD

● Patients with cystic fibrosis may still have a significant degree of steatorrhea despite adequate pancreatic enzyme supplementation. Taurine is a conditionally essential amino acid that possibly improves the micellar phase of fat digestion. Thirteen children with cystic fibrosis and a significant degree of steatorrhea (>13 g/d) were enrolled in a randomized double-blind crossover study of taurine (30 mg/kg per day) in contrast to placebo for two successive 4-month periods. No difference was noted in height and weight velocity, lung function, vitamin A level, and essential fatty acid status. Twelve of the 13 patients showed a decrease in fecal fatty acid excretion (26.5 ± 2.6 g/24 h vs 15.4 ± 2.5 g/24 h), affecting mainly saturates and monounsaturates, and a decrease in total sterol excretion (1492.6 ± 303 mg/24 h vs 1211.7 ± 213.8 mg/24 h) while ingesting taurine. Taurine may be a useful adjunct in patients with cystic fibrosis and severe steatorrhea.

(AJDC. 1991;145:1401-1404)

As a result of studies showing an interdependence between pulmonary disease, pancreatic insufficiency, and nutrition in relation to survival in cystic fibrosis, greater emphasis is now being placed on nutritional supplements and optimal correction of the maldigestion and malabsorption of nutrients.¹

We recently observed that nearly 25% of our patients still have a significant degree (>15 g/d) of steatorrhea despite optimal amounts of Pancrease (pancrelipase).² It therefore is evident that there are still shortcomings of current modalities of treatment. Having previously reported that the lipolytic phase defect secondary to pancreatic lipase and bicarbonate deficiency is compounded by impairment of the micellar phase of digestion,^{3,4} we reasoned that the increased ratio of glycine to taurine-conjugated bile acids secondary to large fecal losses of bile acids^{5,6} could contribute to fat malabsorption.

Taurine-conjugated bile acids have theoretical advantages over glycine conjugates. Their lower pKa (1.8 vs 3.8 to 4.3) keeps them soluble in the acidic duodenum of patients with pancreatic insufficiency.⁷ In contrast to glycine conjugates, which are, in part, passively absorbed in the proximal jejunum, taurine conjugates are mostly absorbed in the ileum.⁸ Taurine is said to be a "conditionally essential" nutrient since needs cannot be met⁹ when taurine intake is inadequate¹⁰ or when bile acid, and therefore, taurine losses are increased as in cystic fibrosis.¹¹

So far, four studies have been conducted to test the hypothesis that taurine supplementation could improve fat absorption. Three articles stated that taurine was effective particularly in patients with more severe steatorrhea,¹²⁻¹⁴ while the only double-blind study failed to show an effect.¹⁵ We herein confirm our earlier reports^{12,13} in a double-blind randomized trial targeted to patients with a significant degree of fat malabsorption.

PATIENTS AND METHODS

Of 33 patients initially screened, 13 (six boys and seven girls) with a mean age of 11.5 years (6.2 to 20.3 years) were included in the study with documentation of a fecal fatty acid excretion in excess of 13 g/d while receiving pancreatic enzyme supplements (pancrelipase). Relevant anthropometric, pulmonary function, and biochemical data are shown in Table 1. None of these patients had evidence of liver disease according to results of tests to check bilirubin, aspartate aminotransferase, γ -glutamyltransferase, and cholestyramine levels, and according to echography. Anthropometric data showed that there was little evidence of growth impairment or malnutrition. However, there was evidence of deficiency of vitamin A as well as essential fatty acid as assessed with ratios previously reported as the most reliable indexes of essential fatty acid deficiency.¹⁶ Dietary records of fat intake were kept by parents and checked by the clinic dietitian. Fat intake averaged 103 ± 13 g/d. The average fat excretion was 27 g with a range of 15 g/d to 51 g/d. The study protocol was approved by the Ethics Committee of Hôpital Ste-Justine (Montreal, Quebec), and consent was obtained from the parents.

The 13 patients were randomly assigned to receive either recrystallized taurine (McNeil Pharmaceutical, Springhouse, Pa) or placebo during an initial 4-month period after which each patient received the alternate supplement during the second 4-month period. Taurine capsules (285 mg each) and placebo (lactose) were prepared by McNeil Pharmaceutical, Spring

Accepted for publication April 8, 1991.

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Table 1.—Clinical and Biological Characteristics of the Patients at Entry in the Study*

Patient No./ Sex/Age, y	Anthropometric Data				γ -GT, U/L	Vitamin A, mg/L	α -Tocopherol Total Lipids, mg/g	Fatty Acid Ratios†	
	Height, % Expected	Weight for Height, % Expected	Shwachman Score	FEF				20:3 n9 20:4 n6	n7 Family 18:2 n6
1/M/8.2	103	98	98	...	8	0.18	2.02	0.057	0.298
2/F/8.7	98	95	90	49	19	0.27	...	0.051	0.226
3/F/11.6	98	98	88	112	20	0.32	1.01	0.163	0.771
4/F/11.9	100	94	87	112	10	0.47	1.69	0.054	0.294
5/F/14.9	98	97	87	75	23	0.34	0.60	0.042	0.308
6/F/20.3	96	134	94	89	9	0.69	1.53	0.05	0.375
7/M/6.3	101	104	92	84	9	0.27	1.90	0.111	0.496
8/M/12	94	100	91	101	8	0.34	0.35	0.067	0.380
9/M/15.7	101	87	96	115	13	0.36	2.02	0.035	0.235
10/F/10.9	88	91	75	...	8	0.25	1.25	0.064	0.407
11/F/10.1	100	95	96	95	21	0.35	2.02	0.033	0.201
12/M/10.8	95	92	82	91	11	0.34	1.56	0.066	0.366
13/M/7.9	88	87	82	82	10	0.37	2.60	0.033	0.291
Mean \pm SE	97 \pm 1.3	97.8 \pm 3.3	89.1 \pm 1.8	91.4 \pm 5.8	13 \pm 5.6	0.35 \pm 0.034	1.55 \pm 0.19	0.064 \pm 0.01	0.358 \pm 0.041
Normal values, (Mean \pm SEM)	100 \pm 5	100 \pm 5	100	100 \pm 5	13 \pm 10	0.55 \pm 0.25	1.44 \pm 0.06	0.016 \pm 0.006	0.11 \pm 0.025

*FEF indicates forced expiratory flow between 25% and 75% of expired vital capacity as percentage of expected value for age; and γ -GT, γ -glutamyl transpeptidase. The mean \pm SE age of the patients in the study is 11.5 \pm 1 years.

†Eicosanoic/arachidic acid (17); and family of n7 fatty acids/linoleic acid (17).

House, Pa, and coded before they were sent to the hospital pharmacy responsible for issuing them to the patients at the time of their regular clinic visits along with pancrelipase capsules, tocopherol acetate (Aquasol E, 200 IU/d), and the daily multivitamin supplement of vitamin A (4000 IU), vitamin D (400 IU), and vitamin C (75 mg). During the two experimental periods, no change was made in the type (pancrelipase) and number of capsules or in the vitamin supplementation program. Six of the 13 patients were administered cloxacillin during the duration of the study. Taurine (30 mg/kg per day) or placebo was administered in fractionated dosages at the same time as pancreatic supplements.

At the end of each treatment period, a questionnaire was given to each parent to be completed before the child's next clinic visit. Total energy and fat intake, frequency and consistency of bowel movements, and whether there was any abdominal pain were recorded. Seventy-two-hour stool and 24-hour urine collections were obtained at the end of each 4-month period. Stools were frozen on evacuation. At the time of clinic appointments, anthropometric data were recorded, a blood sample was obtained, and pulmonary function tests were repeated.

Stool homogenates were used for the gas-liquid chromatography determination of fatty acids as well as neutral and acidic sterols.¹² Stool nitrogen was measured with a modification of the Kjeldahl procedure.¹⁷ Blood collected after an overnight fast in test tubes containing ethylenediaminetetraacetic acid were used for gas-liquid chromatography measurements of fatty acids.¹⁶ Vitamin A levels were determined with spectrophotometry and α -tocopherol levels with high-pressure liquid chromatography.¹⁸ Values for α -tocopherol were expressed in milligrams per gram of total lipids.¹⁹ Urinary taurine was determined with ion exchange chromatography on sulfonated polystyrene beads linked to divinyl benzene using an LKB Alpha Plus 4151 analyzer (LKB Instruments Inc, Gaithersburg, Md) and a Hewlett-Packard 3392 A integrator (Hewlett-Packard Co, Palo Alto, Calif).²⁰

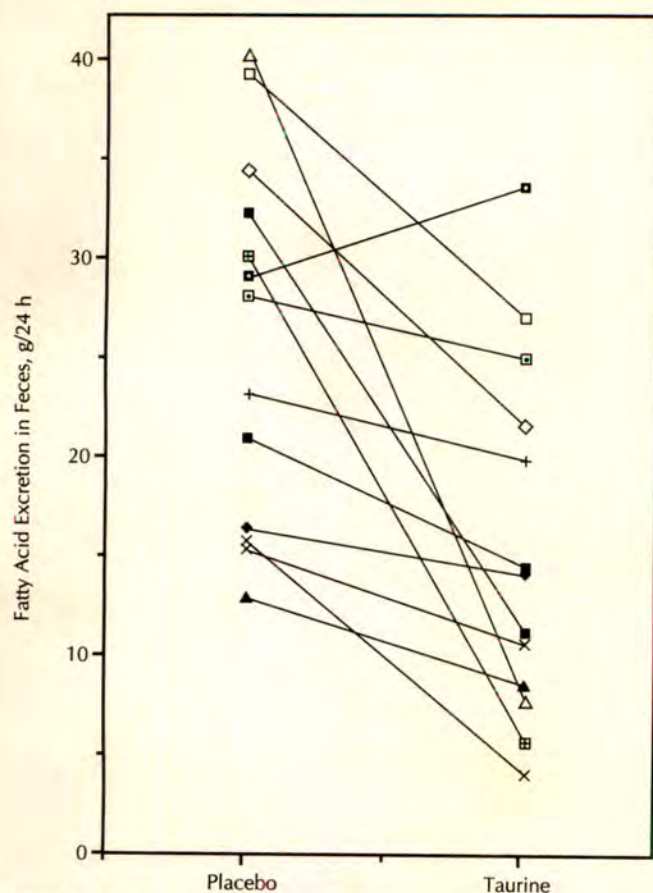
All results, unless otherwise specified, were expressed as mean \pm SE. The response to taurine supplementation was evaluated using paired and unpaired Student's *t* tests as described in the analysis of crossover designs.²¹

RESULTS

The questionnaires that were completed by the parents failed to show a change in the appetite and fat intake of the 13 patients. With regard to digestive symptoms, there was an improvement in the number and consistency of stools as well as a disappearance of abdominal pain in four patients who received taurine supplements, while placebo reportedly produced an improvement in two patients. No difference in height and weight velocities could be documented as a result of taurine supplementation, and no change could be detected in lung function. There was good compliance with the protocol as all patients increased their urinary excretion of taurine. The mean excretion (micromole per millimole of creatinine) was 56.0 \pm 6.9 with placebo and 414.3 \pm 31.2 with taurine supplementation.

The percentage of fat absorption was improved by taurine supplementation (75% \pm 3% vs 86% \pm 2%, *P* < .01). Twelve of the 13 patients showed a decrease in fecal fatty acid excretion (Figure). The overall improvement of more than 40% in fatty acid excretion was highly significant (*P* < .005), but it affected mainly saturated fatty acids (C16:0, C18:0) and the monounsaturate, oleic acid (C18:1, n9); the difference in the mean excretion of linoleic acid was only marginally significant (*P* < .1) (Table 2). Despite the decrease in the loss of lipid nutrients caused by taurine supplements, it failed to improve vitamin A levels and the ratios of fatty acids used as indicators of essential fatty acid deficiency.

As expected, there was a close correlation between fecal fatty acids and nitrogen excretion. However, a paired *t* test (*P* < .1) did not show a statistical difference in nitrogen excretion between the taurine (2.44 \pm 0.33 g/24 h) and the placebo (3.04 \pm 0.44 g/24 h) treatment periods. The effect of taurine on sterol excretion is shown in Table 3. Al-



Individual response of fecal fat excretion obtained from 3-day stool collections carried out following 4 months of treatment with placebo and taurine. Twelve of the 13 patients responded to taurine supplementation ($P < .005$ by paired t test).

Table 2.—Effect of Taurine on the Total and Pattern of Excreted Fatty Acids (n = 13)*

Treatment	16:0	18:0	18:1 (n = 9)	18:2 (n = 6)	Total Fatty Acid Excretion
Placebo	7.5 ± 0.8	7.7 ± 1.6	5.4 ± 1.0	2.4 ± 0.8	26.5 ± 2.6
Taurine	4.8 ± 0.7	4.3 ± 1.2	2.8 ± 0.6	0.9 ± 0.2	15.4 ± 2.5
Paired t test	$P < .05$	$P < .05$	$P < .05$	$P < .1$	$P < .005$

*The individual fatty acids account for nearly 90% of the total fatty acids excreted in the stools. Values are given as mean ± SE and are expressed in grams per 24 h.

Table 3.—Effect of Taurine on Sterol Excretion (n = 13)*

Treatment	Neutral Sterols	Acidic Sterols	Total
Placebo	645.9 ± 155.8	846.7 ± 156.1	1492.6 ± 303.0
Taurine	509.5 ± 97.3	702.2 ± 126.8	1211.7 ± 213.8
Paired t test	NS	NS	$P < .05$

*Values are given as mean ± SE and expressed in milligrams per 24 h. NS indicates not statistically significant.

though no difference was observed in neutral and acidic sterols (bile acids) taken separately, total sterol excretion decreased significantly ($P < .05$) during the taurine treatment period. In addition, there was a close relationship

between bile acid loss and fatty acid malabsorption ($y = 41.5x - 200.8$, $r = .73$, $P < .01$).

COMMENT

This study has shown that a taurine supplement of 30 mg/kg per day administered during a 4-month period in a double-blind crossover trial had an insignificant effect on gastrointestinal manifestations, but led to a significant decrease in both fatty acid and sterol excretion.

Our initial report¹² had shown a more modest effect of taurine, but we had noted (as have others since)¹⁴ that patients with cystic fibrosis and more severe steatorrhea are more likely to ameliorate their condition with the use of taurine supplements. Because of these earlier findings obtained in open trials and in view of a double-blind study conducted in Australia reporting no effect of taurine,¹⁵ we decided to adopt a double-blind randomized design to test the effect of taurine in patients who had significant gastrointestinal manifestations and a significant degree of steatorrhea while receiving a high-energy diet and a liberal intake of lipids.

The reduction in fecal fatty acid excretion coupled with an improvement of fat absorption was impressive. It confirms our earlier findings,¹² as well as those of a study performed in Italy,¹⁴ but is at odds with a double-blind protocol carried out in Australia. The reason for this may well be that patients for that study had a wide range (48% to 96%) of fat absorption. Only seven of their 20 patients had a moderately severe degree ($75.6 \pm 15.6\%$) of fat malabsorption.¹⁵

Because taurine supplementation also decreased total sterol excretion, it can therefore be expected to exert a favorable influence on the interruption of the enterohepatic circulation of bile acids.²² However, in these 13 patients with no evidence of growth impairment or clinical malnutrition, taurine had no effect on growth velocity or weight gain. We recently reported that there was a good correlation between essential fatty acid deficiency and fecal fatty acid loss.²³ However, the present study failed to show an amelioration of the plasma essential fatty acid patterns despite a 40% decrease in steatorrhea. On the other hand, the present findings confirm our initial study¹² that showed that taurine does not appear to improve the absorption of polyunsaturated fatty acid. Its effect is mainly directed to the nonpolar saturates and monounsaturates, which require a higher concentration of bile acids for their incorporation into micelles and are taken up more slowly by the absorptive apparatus than polyunsaturates.²²

Besides the well characterized role of taurine for the conjugation of bile acids in the liver,²⁴ taurine is present in muscle in quantities exceeding those of all other amino acids.²⁵ Taurine has been shown to play a key role in the myocardium,²⁶ to stabilize muscle intracellular membranes,²⁷ and to protect against proteolysis of muscle structural proteins.²⁸ However, a recent study testing the hypothesis that taurine deficiency could contribute to the increased breakdown of proteins in cystic fibrosis failed to show that taurine had any effect on whole-body protein flux, synthesis, and catabolism.²⁹

In the treatment of pancreatic steatorrhea, the challenge is to deliver enough active enzymes to a digestive-absorptive apparatus with a pH close to neutrality. Several factors may be responsible for the persistence of a significant degree of steatorrhea in any patient treated with pancreatic enzymes: the potency and dosage of the

pancreatic enzyme preparation, the acid-secreting status of the patient, and the patient's capacity to compensate for the bile acid loss associated with maldigestion of nutrients.³⁰ The present findings suggest that a hepatic pool of taurine sufficient to maintain a normal glycine-taurine ratio of conjugated bile acids may be an additional factor.

Further studies will be required to define the effect of taurine supplementation on the absorption of lipids and on the metabolism of bile salts before recommending its general use. However, we can conclude from this study, from others published so far,¹²⁻¹⁴ and from our experience over the past few years that taurine is a safe and effective adjuvant in patients with severe steatorrhea who fail to respond to pancreatic enzyme supplements. Only longer periods of treatment will allow conclusions on its effects on nutritional status, growth, and pulmonary function.

This study was supported by the Canadian Cystic Fibrosis Foundation (CCFF) and by McNeil Pharmaceutical, Springhouse, Pa. Dr Smith was the recipient of a CCFF Research Fellowship, and Dr Lacaille received a grant from the Association Française pour la Lutte Contre la Mucoviscidose.

We thank Ronald Sokol, MD, and Iris Osberg of the Pediatric Clinical Center, University of Colorado Health Sciences Center, Denver, for determination of α -tocopherol and total lipid levels. We also thank Robert Giguère, MD, of the Pediatric Department at the University of Sherbrooke, Quebec, for urinary taurine measurements, and Danielle St-Cyr Huot for typing the manuscript.

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Respirosonography in Infants With Acute Bronchiolitis

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● Respirosonography was used to analyze lung sounds and breathing patterns in 16 infants with acute bronchiolitis who were treated with nebulized salbutamol (albuterol). Wheezing was measured as a proportion of respiratory time (time spent wheezing [T_w]/total time [T_{tot}]). A decrease of 10% or greater in T_w/T_{tot} or a reduction in T_w/T_{tot} to less than 2% was considered a positive response to salbutamol. Seven infants responded to the salbutamol, and nine did not. In responders, T_w/T_{tot} decreased from $47\% \pm 26\%$ to $20\% \pm 25\%$ (mean \pm SD), and the respiratory rate decreased from 65 ± 8 to 57 ± 7 breaths per minute. In nonresponders, mean T_w/T_{tot} either did not change or increased, and there was no significant change in respiratory rate (53 ± 10 breaths per minute before salbutamol inhalation and 56 ± 9 breaths per minute after salbutamol inhalation). Complex repetitive waveforms, different from the sinusoidal waveforms of typical wheezing, were observed in 14 of 16 infants. Our findings add supportive evidence to the clinical impression that some infants with bronchiolitis respond to salbutamol. Respirosonography provides a noninvasive method for objective clinical assessment of young, wheezy children.

(AJDC. 1991;145:1405-1410)

Wheezing is a common clinical sign of obstructive airway disease. Wheezes are musical adventitious lung sounds that originate from oscillating airway walls and depend on a critical airflow rate, a critical flutter frequency, and some degree of airway geometry distortion.¹ Several respiratory illnesses during infancy that are associated with airflow obstruction (ie, bronchiolitis, infantile asthma, bronchopulmonary dysplasia, and cystic fibrosis), are accompanied by wheezing. The role of bronchial hyperresponsiveness in the pathogenesis of these conditions is not yet clear. It has been shown that infants with histories of recurrent wheezing episodes may develop airflow obstruction after bronchial provocation with inhaled histamine² or nebulized distilled water.³ However, clinical airway obstruction may not be relieved with nebulized bronchodilators, which indicates a more complex

pathogenesis of airway obstruction in infantile asthma.⁴ While some studies have reported a lack of efficacy of bronchodilators in the treatment of acute wheezing,^{5,6} others have found a beneficial effect.⁷⁻⁹ Generally, pediatricians evaluate the potential role of a bronchodilator by clinically assessing a wheezy infant before and after administration of a trial dose to establish therapeutic benefit before further use.¹⁰

Objective assessment of the response to bronchodilators in patients in this age group is difficult. Most bedside lung function measurements are impractical in infants with acute wheezing. These techniques require sedation, which causes problems in acutely sick infants.¹¹ Therefore, the evaluation of a trial dose of a bronchodilator is usually subjective, being based on changes in respiratory rate, use of accessory muscles, inspiratory-expiratory ratio, presence of cyanosis, and estimation of the severity of wheezing.¹² However, subjective wheeze assessment is flawed by interobserver and intraobserver variability.¹³

Computer-aided analysis of recorded lung sounds is useful as an objective and noninvasive approach to the clinical assessment of wheezy infants. Wheezes present as sharp peaks in the power spectrum that can be detected and measured with automated analysis.¹⁴ In a previous investigation of older asthmatic children before and after exercise,¹⁵ we documented a correlation between the proportion of time spent wheezing and the degree of airway obstruction measured by forced expiratory volume in 1 second (FEV₁), maximum midexpiratory airflow, and specific airway conductance. In the present study, we used digital respirosonography¹⁶ in infants with acute airway obstruction to assess changes in wheeze characteristics before and after bronchodilator treatment. This pilot project was undertaken to define acoustic characteristics of wheezing in infants and to evaluate a potential role for lung sound analysis as a noninvasive method of assessing airway responsiveness in young children.

SUBJECTS AND METHODS

Subjects

Infants younger than age 2 years who were admitted to the Children's Hospital in Winnipeg, Manitoba, between November 1, 1989, and March 15, 1990, with a clinical diagnosis of acute bronchiolitis were studied. Patients for whom salbutamol (albuterol) inhalations were part of the prescribed treatment were included after informed parental consent was obtained. Infants with cystic fibrosis, congenital heart disease, or congenital anomalies of the respiratory system were excluded. Routine vi-

Accepted for publication August 18, 1991.

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Presented at the 56th Annual Scientific Assembly, American College of Chest Physicians, Toronto, Ontario, October 25, 1990.

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Table 1.—Characteristics of Infants With Acute Bronchiolitis*

Patient No.	Sex/ Age, mo	Virus	Associated Problems	No. of Previous Wheezing Episodes
1	M/11	None	FHxA	1
2†	F/1.5	None	BPD	0
3†	M/5	RSV	BPD	>3
4†	F/12	RSV	BPD	>3
5	M/8	Adeno 3	BPD, FHxA	0
6	M/3	RSV	None	0
7	F/21	None	None	0
8	M/10	None	None	0
9	M/15	RSV	None	0
10†	F/6	RSV	FHxA	0
11†	M/1	RSV	None	0
12	M/6	None	FHxA	0
13†	M/23	None	FHxA	1
14	M/5	None	None	1
15†	M/13	None	None	2
16	M/10	Influenza A	FHxA	0

*FHxA indicates family history of asthma; BPD, bronchopulmonary dysplasia; RSV, respiratory syncytial virus; and adeno 3, adenovirus type 3.

†Patients who responded to bronchodilator administration.

ral studies were performed. The personal and family history of asthma, allergies, wheezing episodes, and respiratory tract infections were noted. This study was approved by the Faculty Committee on the Use of Human Subjects in Research.

Study Protocol

Lung sounds were recorded immediately before and 10 to 15 minutes after one salbutamol inhalation. A dose of 0.03 mL of nebulizer solution per kilogram of body weight is routinely used in our institution. The 0.5% nebulizer solution contains 0.9% saline that is added to a total volume of 2 mL. The solution is administered via a face mask with 5 L of oxygen per minute. All patients were awake during lung sound recording. Most of them were resting comfortably on a parent's lap or in bed. Studies performed after salbutamol administration were always conducted with the patient in the same position as before inhalation.

Recording and Analysis of Respiratory Sounds

Lung sounds were recorded as previously described¹⁶: a contact transducer (EMT25C, Elema/Siemens, Iselin, NJ) was attached with double-sided adhesive rings to the anterior or posterior upper chest on the right or to the posterior upper chest on the left. The recording site depended on the patient's most comfortable position during the study. The position of the sound transducer remained unchanged before and after treatment. Respiration signals from the rib cage and abdomen were obtained with uncalibrated respiratory inductive plethysmography (Respirace TM, Ambulatory Monitoring Inc, Ardsley, NY). Sound and respiration signals were simultaneously recorded on a four-channel frequency modulation instrumentation recorder (3960B, Hewlett Packard, Waltham, Mass).

On playback, the sounds were first low-pass filtered with a sixth-order Butterworth filter at 1200 Hz to avoid aliasing during sampling. The signals were played through an analog-to-digital converter (Data Translation 2801a, Marlborough, Mass) into a personal computer compatible with a PC/AT (IBM, Chicago, Ill). The sampling rate was 5120 Hz per channel. A customized computer program¹⁶ was used for data acquisition, analysis, and

display. Fast-Fourier transformation was applied to 1024 data points at 100-ms intervals. This resulted in a 50% overlap into adjacent 100-ms segments, allowing the application of a Hanning window to the data with no loss of information.

Digital respirosograms were produced from the resulting power spectra. Any particular 100-ms segment could be highlighted and viewed in detail in both the time and the frequency domains, and any part of the data could be selected for digital-to-analog conversion and playback through a loudspeaker or headphones.

For each infant, 10 to 15 seconds of continuous lung sounds before and after salbutamol administration were chosen for analysis. The selection of sound from the recording was based on absence of artifacts such as movement, crying, and environmental noise. Consecutive segments of 100 ms were marked as wheezing or normal based on (1) the distinct peaks in the frequency domain, (2) periodic waveform appearance in the time domain, and (3) auditory verification on playback. Wheezing was measured as a proportion of total respiratory time (time spent wheezing [T_w]/total time [T_{tot}]). The average peak frequency of the wheezing ($avgF_w$) was computed for each recording. Respiratory rate and ventilatory timing components (inspiration-expiration ratio) were measured from the plethysmographic signals. We arbitrarily defined a decrease of 10% or greater in T_w/T_{tot} or a reduction in T_w/T_{tot} to less than 2% as positive responses to salbutamol.

We used unpaired, two-tailed Student's *t* tests to compare the T_w/T_{tot} , $avgF_w$, respiratory rate, and inspiration-expiration ratios of responders with those of nonresponders. We also compared results before and after salbutamol administration using paired *t* tests. Statistical significance was accepted as $P < .05$. The data are presented as means \pm SDs.

RESULTS

Sixteen infants (12 boys) with a mean age of 9.4 months (range, 1 to 23 months) were enrolled in this study. Results of viral studies revealed the presence of a virus in half the infants. Six infants had respiratory syncytial virus; one, adenovirus type 3; and one, influenza A. Four of the infants also had histories of bronchopulmonary dysplasia. Asthma was present in first-degree relatives of six patients, and six patients had histories of wheezing episodes (Table 1).

Based on our definition of a 10% or greater reduction in T_w/T_{tot} or a reduction in T_w/T_{tot} to less than 2% after salbutamol administration, seven infants were classified as responders and nine as nonresponders (Fig 1). Patient characteristics, such as age, gender, family history of asthma, and presence of viruses were not markedly different between the two groups (Table 2). Responders had a significant decrease in respiratory rate (from 65 ± 8 to 57 ± 7 breaths per minute; $P < .05$) after salbutamol administration, whereas respiratory rate in nonresponders remained essentially unchanged (from 53 ± 10 to 56 ± 9 breaths per minute; Fig 2). The inspiration-expiration ratio was similar in both groups (0.7 ± 0.2 and 0.7 ± 0.1 , in responders and nonresponders, respectively), and did not change after salbutamol administration in either group. In responders, T_w/T_{tot} decreased from $47\% \pm 26\%$ to $20\% \pm 25\%$, with no significant change in $avgF_w$ (230 ± 5 Hz and 255 ± 101 Hz, before and after salbutamol inhalation, respectively). By definition, nonresponders had an unchanged or even greater T_w/T_{tot} after treatment compared with pretreatment values ($31\% \pm 13\%$ vs $38\% \pm 12\%$), but their $avgF_w$ decreased significantly from 271 ± 64 Hz to 206 ± 21 Hz after treatment ($P < .03$; Fig 3). In four children, T_w/T_{tot} increased 10% or greater after salbutamol administration (Fig 1). There was no significant difference in res-

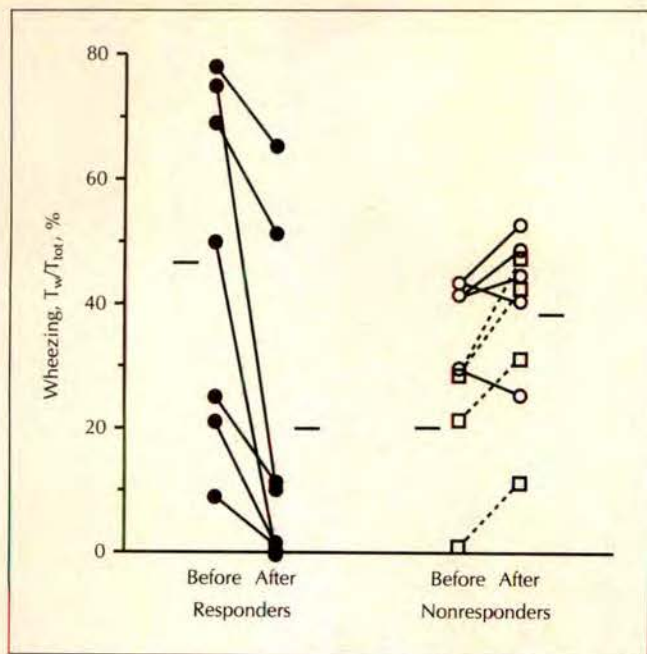


Fig 1.—Changes in time spent wheezing (T_w/T_{tot}) before and after salbutamol inhalation. Group means are indicated by horizontal lines. Among nonresponders, patients with less than a 10% increase in T_w/T_{tot} are indicated by open circles and solid lines, while those with increases in T_w/T_{tot} of 10% or more are shown by open squares and dashed lines.

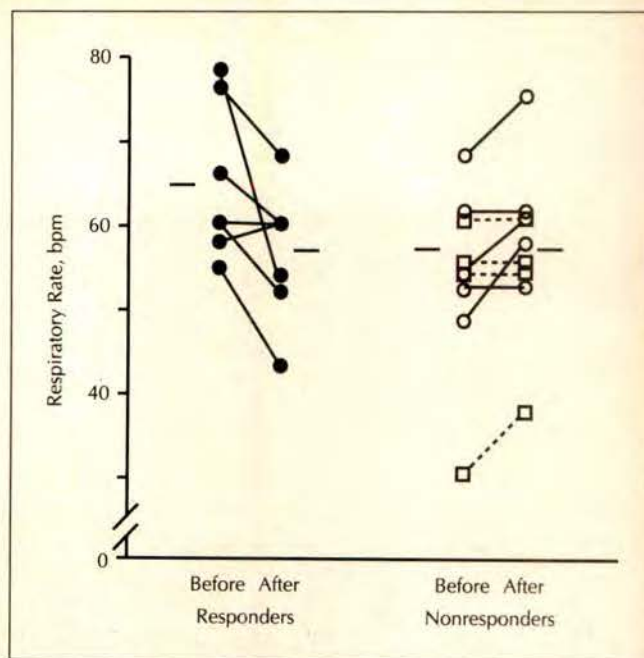


Fig 2.—Changes in respiratory rate before and after salbutamol inhalation (bpm indicates breaths per minute). Among nonresponders, patients with a paradoxical increase in wheezing of 10% or greater are indicated by open squares and dashed lines.

Table 2.—Characteristics of Responders and Non-Responders Before and After Bronchodilator Administration*

Characteristic	Responders (n = 7)		Nonresponders (n = 9)	
	Before	After	Before	After
Respiratory rate, breaths per minute	64.7 ± 8.4	56.7 ± 7.3†	53.3 ± 9.9	56.4 ± 9.2
Inspiration-expiration ratio	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1
T_w/T_{tot} , %	47 ± 26	20 ± 25	31 ± 13	38 ± 12
avgF _w , Hz	230 ± 35	255 ± 101	271 ± 64†‡	206 ± 21

*The mean age (range) was 8.8 months (1 to 23 months) in responders and 9.9 months (3 to 21 months) in nonresponders. Values are means ± SEMs. T_w/T_{tot} indicates time spent wheezing divided by total time, and avgF_w, average peak frequency of wheezing.

† $P < .05$.

‡Data from one patient were excluded.

piratory rate after inhalation in these four patients (Fig 2). In one patient (number 9, Table 1) who underwent evaluation on admission, salbutamol caused an increase in T_w/T_{tot} from 1% before treatment to 11% after treatment. Because wheezing was almost absent before therapy, this patient's data were excluded from the comparison of avgF_w between responders and nonresponders (Fig 3). Sinusoidal waveforms of typical wheezing were easily identified (Fig 4), but complex repetitive waveforms were present in 14 of the 16 infants (Fig 5).

COMMENT

Wheezing in infancy is not well defined. Although the term *wheezy infant* is commonly used to characterize young

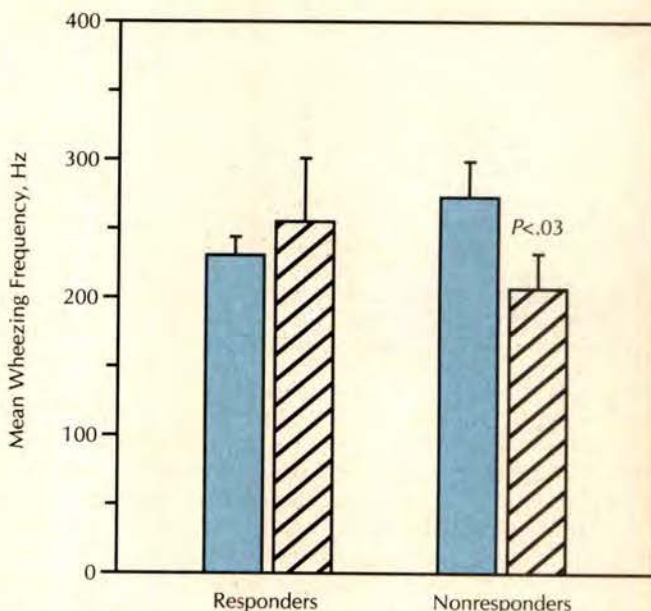


Fig 3.—Changes (mean ± SEM) in wheezing frequency before (shaded bars) and after (hatched bars) salbutamol inhalation. One patient (number 9, Table 1) was excluded from the nonresponders.

patients with a variety of obstructive lung diseases, we are not aware of published data that describe the acoustic characteristics of adventitious lung sounds in this age group. Recent advances in computer technology have made it possible for acoustic measurements of respiration to be conveniently performed using a personal computer.¹⁶

We used a customized computer program (Respiration Acoustics Laboratory Environment, Medi-Wave Inc, Winnipeg, Manitoba) for digital respirosography and found that wheezes in infants have different acoustic characteristics than those in older patients. Wheezing in

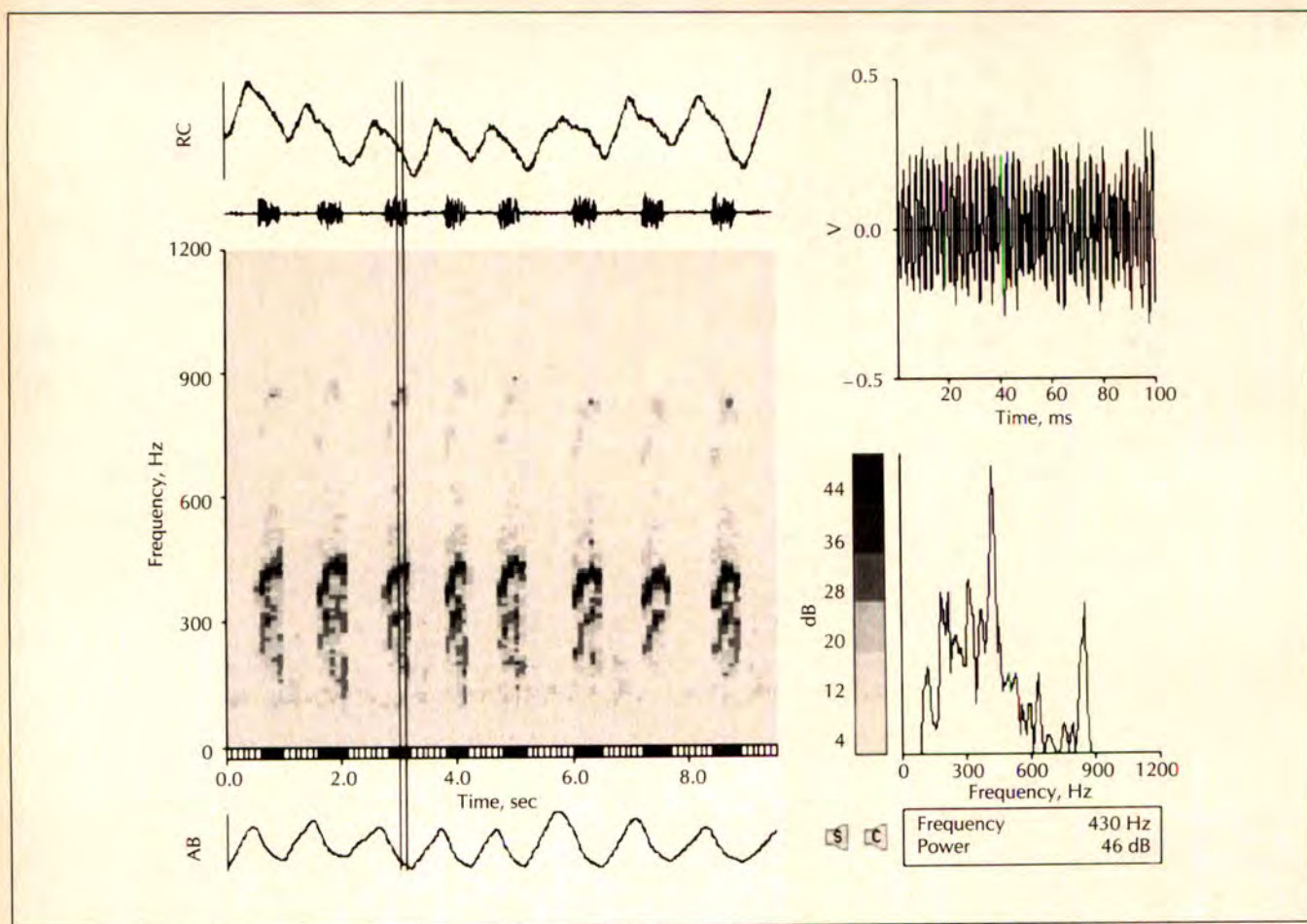


Fig 4.—Digital respirosoundgram showing 9.5 seconds of recorded lung sounds and breathing patterns from patient 8 (Table 1) before salbutamol inhalation. Rib cage (RC) and abdominal (AB) movement are plotted at the top and bottom, respectively. Inspiration is on the upward slope and expiration on the downward slope. The sonogram shows time on the horizontal axis and sound frequency on the vertical axis. Sound intensity is displayed as shades (black, loud; gray, medium; and white, low). The vertical double bar at 3.1 seconds highlights 100 ms of sound during expiration. A time amplitude plot of the sound wave (top right) and the respective Fourier spectrum (bottom right) show this 100-ms segment in detail. Typical wheezing, commonly seen in older patients with asthma, is present in this infant. There are distinct peaks in the power spectrum, a sinusoidal waveform in the time domain, and a concentration of sound intensity in a narrow frequency band on the sonogram. All segments containing wheezes are shaded in gray on the horizontal axis.

older asthmatic patients is typically a continuous musical sound that appears as a concentration of sound intensity at distinct frequencies.^{14,17} In the power spectrum, wheezing presents as one or more sharp peaks that can be detected and measured with automated analysis.¹⁸ In infants with acute bronchiolitis, wheezes did not always present as sharp peaks. In 14 of 16 patients, complex repetitive waveforms were the dominant pattern (Fig 5). To the subjective listener, these sounds appear less musical and more raspy and are frequently concurrent with coarse crackles. Therefore, automated wheeze characterization with fast-Fourier transformation, based only on the detection of spectral peaks, is unreliable in infants. In addition to power spectral analysis, we studied lung sounds in the time domain with expanded waveform analysis.¹⁹ We found that a combination of waveform assessment in the time domain, peak detection in the frequency domain, and auditory verification on playback, were necessary to characterize and measure wheezing in young infants.

Baughman and Loudon¹⁴ analyzed lung sounds of adult patients with acute asthma. They used T_w/T_{tot} as an acoustic parameter that indicated the severity of airway obstruction and found a significant correlation between

FEV_1 and T_w/T_{tot} . In asthmatic children with postexertional asthma, we also observed a significant correlation between T_w/T_{tot} and severity of airway obstruction as measured considering FEV_1 , maximum midexpiratory airflow, and specific airway conductance.¹⁵ In the present study, we documented a decrease in T_w/T_{tot} of 10% or greater or a reduction in T_w/T_{tot} to less than 2% after salbutamol inhalation in seven of the 16 infants. We chose this definition of a positive response to salbutamol because a change in T_w/T_{tot} of 10% or greater would likely be noticed on subjective auscultation¹³ and because false-positive wheeze detection using spectral characterization has occurred in fewer than 3% of patients tested in our laboratory.¹⁸ In our study, the significantly lower respiratory rate of patients who wheezed less after salbutamol inhalation also indicates less airflow obstruction. There is no evidence that wheeze duration depends on respiratory rate. If there were a relationship between breathing pattern and duration of wheeze, one would expect rapid, shallow breathing to produce less wheezing than slower and deeper breathing because wheeze generation requires critical transpulmonary pressures and airway deformation.¹

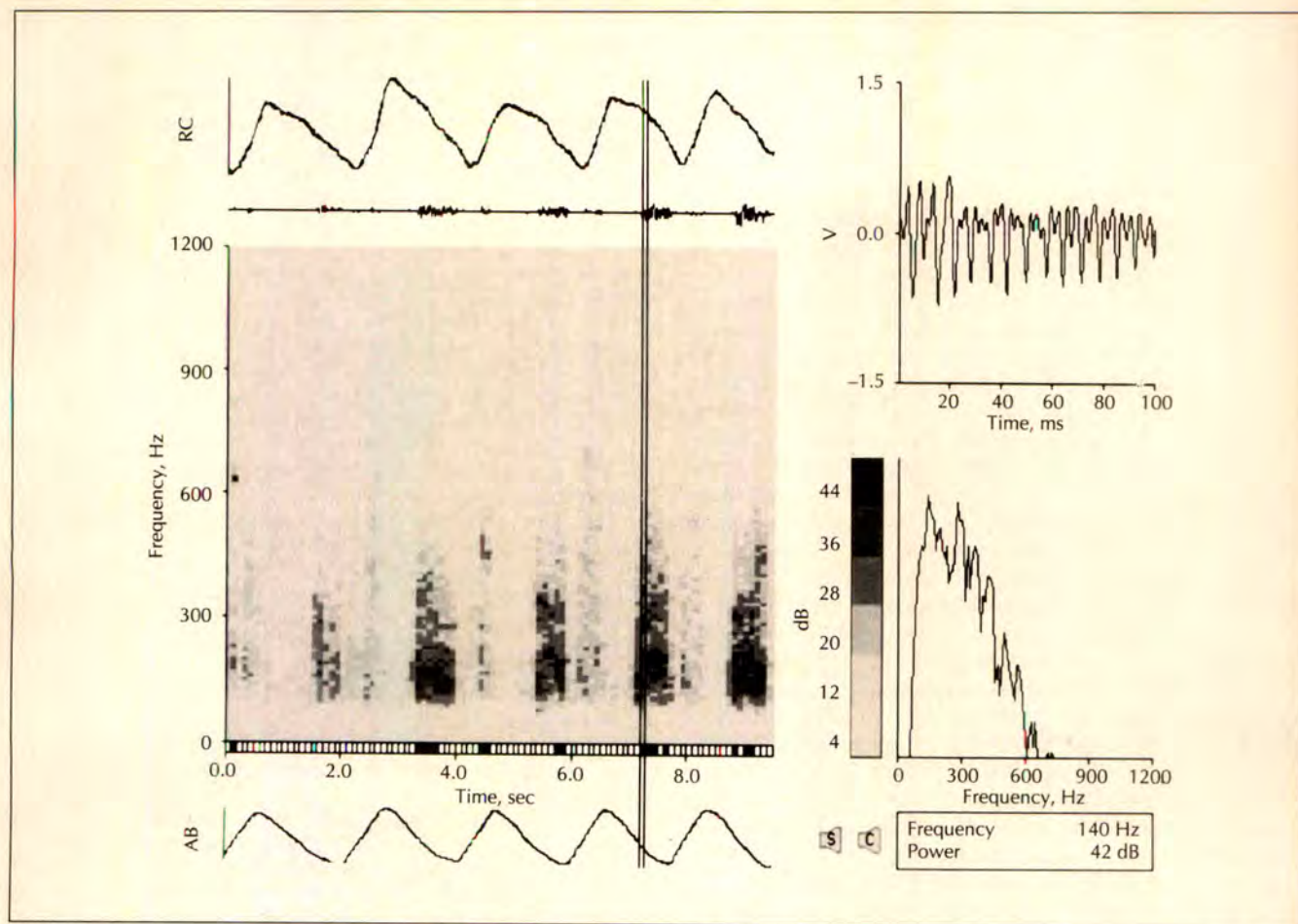


Fig 5.—Digital respirosoundgram as described in Fig 4 showing 9.5 seconds of recorded lung sounds and breathing patterns from patient 13 (Table 1) before salbutamol inhalation. The vertical double bar at 7.3 seconds points to a 100-ms segment of wheezing during expiration. The time amplitude display (top right) shows a complex repetitive wave form. The Fourier spectrum (bottom right) has fewer distinct peaks than that in Fig 4. One hundred-millisecond time intervals during which wheezing occurred are marked in gray on the horizontal axis.

The efficacy of inhaled bronchodilators in infants with acute bronchiolitis is still controversial.^{4,6} Although the relationship between airway hyperresponsiveness in infancy and symptomatic airway disease is not well determined, recent studies^{7-9,20} indicate that many infants with wheezing will improve if treated with bronchodilators regardless of whether they are classified as having asthma, bronchiolitis, or wheezing-associated respiratory illness.²¹

Some infants may experience a paradoxical deterioration in lung function after salbutamol inhalation.^{22,23} We found significantly increased wheezing after salbutamol inhalation in four of 16 infants. The respiratory rate remained unchanged after salbutamol inhalation in three of these four infants. In very severe airflow obstruction, normal lung sounds may be of very low intensity, and wheezing may be absent. Under these circumstances, improvement after bronchodilator administration may be accompanied by wheezing. However, these infants had normal vesicular lung sound intensity before inhalation. By both clinical and respirosoundgraphic analysis, these patients did not improve after salbutamol inhalation, but whether increased wheezing reflected a paradoxical response remains unclear.

Baughman and Loudon¹⁴ found that adult subjects with asthma and increased FEV₁ after bronchodilator administration experienced a reduction in the sound frequency of

the highest pitched wheeze.¹⁴ It is not clear from their data whether a reduction of T_w/T_{tot} in their patients correlated with the reduction in wheeze frequency. In a previous study,¹⁵ we could not demonstrate a relationship between T_w/T_{tot} and wheeze frequency. In our present study of wheezy infants, we found that, after salbutamol inhalation, four of the responders had a reduction in $avgF_w$, two showed an increase in $avgF_w$, and one had no wheezing. It is interesting that wheeze frequency decreased after salbutamol inhalation even among nonresponders (seven of nine patients). At present, it is unclear whether a reduction in wheeze frequency indicates an improvement in the airflow obstruction or is caused by another mechanism.

The graphic display of lung sounds and respiration curves from the rib cage and abdomen shown in Figs 4 and 5 contains most parameters commonly used in the clinical scoring of wheezy infants. In fact, only the patient's oxygenation, which is generally addressed in clinical scores through an assessment of cyanosis, cannot be derived from the parameters recorded in our study. While oximetry is useful for the initial assessment of severity in bronchiolitis,^{24,25} it may not reflect improvement after treatment.²⁰ In older children with asthma, we found that oxygen saturation may actually decrease immediately after salbutamol inhalation.²⁶

In addition to the respiratory rate and ventilatory tim-

ing components, thoracoabdominal asynchrony is a parameter of airway obstruction that can be measured using respirosography. Clinically, this would reflect chest wall retractions. Allen and coworkers²⁷ have recently measured thoracoabdominal asynchrony in infants with airflow obstruction as the phase shift between the rib cage and abdominal expansion. They demonstrated that improvement of airflow obstruction after bronchodilator administration caused the rib cage and abdomen to move more synchronously. The improvement in chest wall asynchrony was closely related to an improvement in lung mechanics. However, as in other studies of lung function in infants, these authors had to sedate their patients. Reliable recording of both rib cage and abdominal expansion was not achieved in all of our patients, but may be possible in awake infants if they are comfortably seated or positioned in bed. Therefore, measurement of thoracoabdominal asynchrony may be added to lung sound analysis for a comprehensive but noninvasive study of airway responsiveness in young infants.

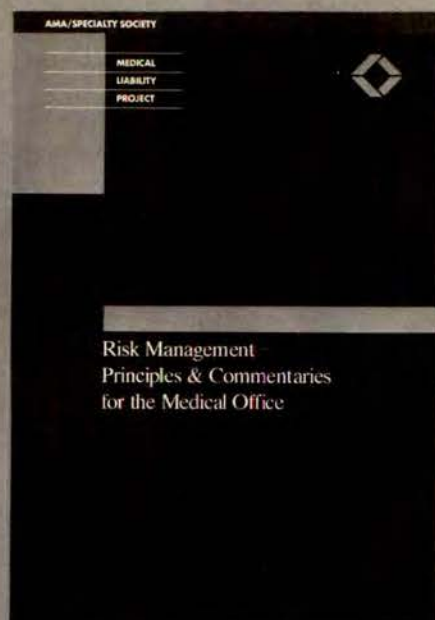
Digital respirosography is a promising new method for the noninvasive clinical assessment of airway responsiveness in young, wheezy infants. Without acoustical standards, the characterization of a young patient as a "wheezy infant" is necessarily imprecise. Such generalized classifications obscure important epidemiologic and therapeutic aspects of obstructive lung disease in young children. Because wheezing in infants appears to have different acoustic characteristics than wheezing in older patients with asthma, the mechanisms for these musical adventitious sounds may also be different. We believe that objective studies of respiration acoustics in wheezy infants will provide a better understanding of the pathophysiology of obstructive airway diseases developing at this young age.

This study was supported by the Children's Hospital of Winnipeg Research Foundation and the Manitoba Health Research Council, Winnipeg.

We thank Victor Chernick, MD, for his helpful suggestions and review of our article and Doris Jensen for secretarial support.

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12 Sections

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IPOL (POLIOVIRUS VACCINE INACTIVATED)

DESCRIPTION: IPOL™, Poliovirus Vaccine Inactivated, produced by Pasteur Mérieux Sérums & Vaccins S.A., is a sterile suspension of three types of poliovirus: Type 1 (Mahoney), Type 2 (MEF-1), and Type 3 (Saukett). The viruses are grown in cultures of VERO cells, a continuous line of monkey kidney cells, by the microcarrier technique. The viruses are concentrated, purified, and made noninfectious by inactivation with formaldehyde. Each sterile immunizing dose (0.5 ml) of trivalent vaccine is formulated to contain 40 D antigen units of Type 1, 8 D antigen units of Type 2, and 32 D antigen units of Type 3 poliovirus, determined by comparison to a reference preparation. The poliovirus vaccine is dissolved in phosphate buffered saline. Also present are 0.5% of 2-phenoxethanol and a maximum of 0.02% of formaldehyde per dose as preservatives. Neomycin, streptomycin and polymyxin B are used in vaccine production, and although purification procedures eliminate measurable amounts, less than 5 ng neomycin, 200 ng streptomycin and 25 ng polymyxin B per dose may still be present. The vaccine is clear and colorless and should be administered subcutaneously.

CLINICAL PHARMACOLOGY: IPOL is a highly purified, inactivated poliovirus vaccine produced by microcarrier culture.^{1,2} This culture technique and improvements in purification, concentration and standardization of poliovirus antigen have resulted in a more potent and more consistently immunogenic vaccine than the Poliovirus Vaccine Inactivated which was available in the U.S. prior to 1988. These new methods allow for the production of vaccine that induces antibody responses in most children after administering fewer doses³ than with vaccine available prior to 1988.

Studies in developed³ and developing^{4,5} countries with a similar inactivated poliovirus vaccine produced by the same technology have shown that a direct relationship exists between the antigenic content of the vaccine, the frequency of seroconversion, and resulting antibody titer.

A study in the U.S. was carried out, which involved 219 two-month-old infants who had received three doses of Poliovirus Vaccine Inactivated manufactured by the same process as IPOL except the cell substrate was primary monkey kidney cells. Seroconversion to all three types of poliovirus was demonstrated in 99% of these infants after two doses of vaccine. Following a third dose of vaccine at 18 months of age, high titers of neutralizing antibody were present in 99.1% of children to Type 1 and 100% of children to Types 2 and 3 polioviruses.⁶

Additional studies were carried out in the U.S. with IPOL. Results were reported for 120 infants who received two doses of IPOL at 2 and 4 months of age. Of these 120 children, detectable serum neutralizing antibody was induced after two doses of vaccine in 98.3% (Type 1), 100% (Type 2) and 97.5% (Type 3) of the children. In 83 children receiving three doses at 2, 4, and 12 months of age detectable serum neutralizing antibodies were detected in 97.6% (Type 1) and 100% (Types 2 and 3) of the children.^{7,8}

Poliovirus Vaccine Inactivated reduces pharyngeal excretion of poliovirus.⁹⁻¹² Field studies in Europe have demonstrated immunity in populations thoroughly immunized with another IPV.¹³⁻¹⁷ A survey of Swedish children and young adults given a Swedish IPV demonstrated persistence of circulating antibodies for at least 10 years to all three types of poliovirus.¹³

Paralytic polio has not been reported in association with administration of Poliovirus Vaccine Inactivated.

INDICATIONS AND USAGE: Poliovirus Vaccine Inactivated is indicated for active immunization of infants, children and adults for the prevention of poliomyelitis. Recommendations on the use of live and inactivated poliovirus vaccines are described in the ACIP Recommendations^{18,19} and the 1988 American Academy of Pediatrics Red Book.²⁰

INFANTS, CHILDREN AND ADOLESCENTS

General Recommendations: It is recommended that all infants, unimmunized children and adolescents not previously immunized be vaccinated routinely against paralytic poliomyelitis.¹⁸ Poliovirus Vaccine Inactivated should be offered to individuals who have refused Poliovirus Vaccine Live Oral Trivalent (OPV) or in whom OPV is contraindicated. Parents should be adequately informed of the risks and benefits of both inactivated and oral polio vaccines so that they can make an informed choice (Report of An Evaluation of Poliomyelitis Vaccine Policy Options, Institute of Medicine, National Academy of Sciences, Washington, D.C., 1988).

OPV should not be used in households with immunodeficient individuals because OPV is excreted in the stool by healthy vaccinees and can infect an immunocompromised household member, which may result in paralytic disease. In a household with an immunocompromised member, only Poliovirus Vaccine Inactivated should be used for all those requiring poliovirus immunization.²⁰

Children incompletely immunized: Children of all ages should have their immunization status reviewed and be considered for supplemental immunization as follows for adults. Time intervals between doses longer than those recommended for routine primary immunization do not necessitate additional doses as long as a final total of four doses is reached (see DOSAGE AND ADMINISTRATION).

Previous clinical poliomyelitis (usually due to only a single poliovirus type) or incomplete immunization with OPV are not contraindications to completing the primary series of immunization with Poliovirus Vaccine Inactivated.

ADULTS

General Recommendations: Routine primary poliovirus vaccination of adults (generally those 18 years of age or older) residing in the U.S. is not recommended. Adults who have increased risk of exposure to either vaccine or wild poliovirus and have not been adequately immunized should receive polio vaccination in accordance with the schedule given in the DOSAGE AND ADMINISTRATION section.¹⁸

The following categories of adults run an increased risk of exposure to wild polioviruses:¹⁹

- Travelers to regions or countries where poliomyelitis is endemic or epidemic.
- Health care workers in close contact with patients who may be excreting polioviruses.
- Laboratory workers handling specimens that may contain polioviruses.
- Members of communities or specific population groups with disease caused by wild polioviruses.
- Incompletely vaccinated or unvaccinated adults in a household (or other close contacts) with children given OPV provided that the immunization of the child can be assured and not unduly delayed. The adult should be informed of the small OPV related risk to the contact.

IMMUNODEFICIENCY AND ALTERED IMMUNE STATUS

Patients with recognized immunodeficiency are at greater risk of developing paralysis when exposed to live poliovirus than persons with a normal immune system. Under no circumstances should oral live poliovirus vaccine be used in such patients or introduced into a household where such a patient resides.¹⁸

Poliovirus Vaccine Inactivated should be used in all patients with immunodeficiency diseases and members of such patients' households when vaccination of such persons is indicated. This includes patients with asymptomatic HIV infection, AIDS or AIDS Related Complex, severe combined immunodeficiency, hypogammaglobulinemia, or agammaglobulinemia; altered immune states due to diseases such as leukemia, lymphoma, or generalized malignancy; or an immune system compromised by treatment with corticosteroids, alkylating drugs, antineoplastic or radiation. Patients with an altered immune state may or may not develop a protective response against paralytic poliomyelitis after administration of Poliovirus Vaccine Inactivated.²¹

CONTRAINDICATIONS: Poliovirus Vaccine Inactivated is contraindicated in persons with a history of hypersensitivity to any component of the vaccine, including neomycin, streptomycin and polymyxin B.

If anaphylaxis or anaphylactic shock occurs within 24 hours of administration of a dose of vaccine, no further doses should be given.

Vaccination of persons with any acute, febrile illness should be deferred until after recovery; however, minor illnesses such as mild upper respiratory infections are not in themselves reasons for postponing vaccine administration.

WARNINGS: Neomycin, streptomycin, and polymyxin B are used in the production of this vaccine. Although purification procedures eliminate measurable amounts of these substances, traces may be present (see DESCRIPTION) and allergic reactions may occur in persons sensitive to these substances.

PRECAUTIONS: General: Before injection of the vaccine, the physician should carefully review the recommendations for product use and the patient's medical history including possible hypersensitivities and side effects that may have occurred following previous doses of the vaccine.

Epinephrine hydrochloride (1:1000) and other appropriate agents should be available to control immediate allergic reactions.

Concerns have been raised that stimulation of the immune system of a patient with HIV infection by immunization with inactivated vaccines might cause deterioration in immunologic function. However, such effects have not been noted thus far among children with AIDS or among immunosuppressed individuals after immunizations with inactivated vaccines. The potential benefits of immunization of these children outweigh the undocumented risk of such adverse events.¹⁸

Drug Interactions: There are no known interactions of Poliovirus Vaccine Inactivated with drugs or foods. Simultaneous administration of other parenteral vaccines is not contraindicated.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to evaluate carcinogenic potential or impairment of fertility have not been conducted.

PREGNANCY: REPRODUCTIVE STUDIES — PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with Poliovirus Vaccine Inactivated. It is also not known whether Poliovirus Vaccine Inactivated can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Poliovirus Vaccine Inactivated should be given to a pregnant woman only if clearly needed.

PEDIATRIC USE: Safety and efficacy of IPOL have been shown in children 6 weeks of age and older^{8,9} (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: In earlier studies with the vaccine grown in primary monkey kidney cells, transient local reactions at the site of injection were observed during a clinical trial.⁶ Erythema, induration and pain occurred in 3.2%, 1% and 13%, respectively, of vaccinees within 48 hours post-vaccination. Temperatures $\geq 39^{\circ}\text{C}$ ($\geq 102^{\circ}\text{F}$) were reported in up to 38% of vaccinees. Other symptoms noted included sleepiness, fussiness, crying, decreased appetite, and spitting up of feedings. Because Poliovirus Vaccine Inactivated was given in a different site but concurrently with Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (DTP), systemic reactions could not be attributed to a specific vaccine. However, these systemic reactions were comparable in frequency and severity to that reported for DTP given without IPV.

In another study using IPOL in the United States, there were no significant local or systemic reactions following injection of the vaccine. There were 7% (6/86), 12% (8/65) and 4% (2/45) of children with temperatures over 100.6°F following the first, second and third doses respectively. Most of the children received DTP at the same time as IPV and therefore it was not possible to attribute reactions to a particular vaccine; however, such reactions were not significantly different than when DTP is given alone.

Although no causal relationship between Poliovirus Vaccine Inactivated and Guillain-Barré Syndrome (GBS) has been established,²² GBS has been temporally related to administration of another Poliovirus Vaccine Inactivated.

NOTE: The National Childhood Vaccine Injury Act of 1986 requires the keeping of certain records and the reporting of certain events occurring after the administration of vaccine, including the occurrence of any contraindicating reaction. Poliovirus Vaccines are listed vaccines covered by this Act and health care providers should ensure that they comply with the terms thereof.²³

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and/or discoloration prior to administration. If these conditions exist, vaccine should not be administered.

After preparation of the injection site, immediately administer the vaccine subcutaneously. In infants and small children, the mid-lateral aspect of the thigh is the preferred site. In adults the vaccine should be administered in the deltoid area.

Care should be taken to avoid administering the injection into or near blood vessels and nerves. After aspiration, if blood or any suspicious discoloration appears in the syringe, do not inject but discard contents and repeat procedures using a new dose of vaccine administered at a different site.

DO NOT ADMINISTER VACCINE INTRAVENOUSLY.

CHILDREN

Primary Immunization: A primary series of IPOL consists of three 0.5 ml doses administered subcutaneously. The interval between the first two doses should be at least four weeks, but preferably eight weeks. The first two doses are usually administered with DTP immunization and are given at two and four months of age. The third dose should follow at least six months but preferably 12 months after the second dose. It may be desirable to administer this dose with MMR and other vaccines, but at a different site, in children 15-18 months of age. All children who received a primary series of Poliovirus Vaccine Inactivated, or a combination of IPV and OPV, should be given a booster dose of OPV or IPV before entering school, unless the final (third dose) of the primary series was administered on or after the fourth birthday.¹⁸

The need to routinely administer additional doses is unknown at this time.¹⁸

A final total of four doses is necessary to complete a series of primary and booster doses. Children and adolescents with a previously incomplete series of IPV should receive sufficient additional doses to reach this number.

ADULTS

Unvaccinated Adults: For unvaccinated adults at increased risk of exposure to poliovirus, a primary series of Poliovirus Vaccine Inactivated is recommended. While the responses of adults to primary series have not been studied, the recommended schedule for adults is two doses given at a 1 to 2 month interval and a third dose given 6 to 12 months later. If less than 3 months but more than 2 months are available before protection is needed, 3 doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. Likewise, if only 1 or 2 months are available, two doses of Poliovirus Vaccine Inactivated should be given at least 1 month apart. If less than 1 month is available, a single dose of either OPV or IPV is recommended.

Incompletely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have had at least one dose of OPV, fewer than 3 doses of conventional IPV or a combination of conventional IPV or OPV totalling fewer than 3 doses should receive at least 1 dose of OPV or Poliovirus Vaccine Inactivated. Additional doses needed to complete a primary series should be given if time permits.

Completely Vaccinated Adults: Adults who are at an increased risk of exposure to poliovirus and who have previously completed a primary series with one or a combination of polio vaccines can be given a dose of either OPV or IPV.¹⁹

HOW SUPPLIED: Syringe, 0.5 ml with integrated needle (1 x 1 Dose package and 10 x 1 Dose package) — Product Nos. 49281-8605-1 and 49281-8605-2.

STORAGE: The vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F and 46°F). The vaccine must not be frozen.

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Manufactured by:
PASTEUR MÉRIEUX Sérums & Vaccins S.A.
Lyon, France
U.S. License No. 384

Product Information
as of December 1990

Printed in U.S.A.

Distributed by:
CONNAUGHT LABORATORIES, INC.
Swiftwater, Pennsylvania 18370
800-VACCINE/800-822-2463

2-101

Neuroblastoma Screening Data

An Epidemiologic Analysis

Steven N. Goodman, MD, MHS, PhD

• Neuroblastoma is one of the most common malignant neoplasms in children under age 5 years. Little progress has been made in the prognosis of advanced stage disease in the past three decades. Since the development in the 1960s of a simple urine test to detect neuroblastoma metabolites, there has been hope that mortality from this disease could be reduced by early detection via mass screening of young infants. Encouraging reports from Japan on mass screening programs instituted in the 1970s have been appearing in the medical literature since 1982, resulting in widespread interest in screening. This article applies standard epidemiologic criteria for screening evaluations to the Japanese reports. We find that the data needed to definitively assess the value of screening were not a part of those reports and that the benefits claimed from the reported data could be due to overdiagnosis. In addition, the most recent Japanese data, combined with recent advances in biologic understanding of neuroblastoma, show that screening at age 6 months may not detect tumors with poor prognoses. Even if it could, it is uncertain whether those outcomes could be substantially altered by earlier diagnosis. Although a final verdict on the value of neuroblastoma screening is not yet possible, these neuroblastoma studies are an excellent example of how screening results must be viewed with extreme caution in the absence of age-specific, population-based incidence and mortality rates.

(*AJDC*. 1991;145:1415-1422)

Neuroblastoma, one of the most common cancers of early childhood, ranks in incidence just below leukemias and approximately equal to brain tumors among children younger than 5 years.¹ In spite of intensive research and new chemotherapeutic regimens, long-term survival from advanced-stage disease has stayed relatively constant at about 10% to 20% in the past three decades.²⁻⁴ Since the development in the 1960s of a simple urine spot test for the excreted metabolites of neuroblastoma, there has been hope that the mortality from this childhood cancer could be reduced through screening.⁵ The basic rationale for such screening was simple: the tu-

mor was thought to be present at birth, and both early stage and young age were associated with excellent prognosis. If the tumor could be detected biochemically at an age when there was known to be excellent survival, we should, in theory, be able to prevent the mortality usually accompanying clinical presentation at a later age. This offered the first possibility that a potentially fatal pediatric disease could be detected and cured via mass screening after the neonatal period.

This reasoning led Japanese investigators to institute experimental screening programs in Japan in the early 1970s. These programs were expanded to eight Japanese regions by the end of that decade, in a consortium known as the Japanese Mass Screening Study Group (MSSG). The first English language report on the Kyoto (Japan) experience was published by Sawada et al⁶ in 1982. This, along with later encouraging reports on the apparent successes of the Japanese screening, led to great enthusiasm for the test both inside and outside that country. By 1985, the results were deemed so convincing within Japan that neuroblastoma screening in 6-month-old infants became recommended as part of their well-child care program, with each prefecture administering its own program.

With increasing awareness of the Japanese experience, scientists in North America and Europe began to call for an examination of neuroblastoma screening in settings outside Japan.² Although one such trial is currently under way in Canada⁷ and another proposed for Britain,⁸ there have been calls in both the medical literature and lay press for the institution of mass screening (*Palm Beach Post*. June 7, 1990:D1).⁹ There also have been anecdotal reports of pediatricians and informed laypeople pressuring regional health departments or taking on themselves the task of organizing local screening programs.

This ground swell was based mainly on the perception that the Japanese screening programs were an unqualified success. This existed partially because of an absence of close examinations of the screening data using well-established epidemiologic criteria. Starting in the late 1980s, investigators began publishing cautions that the data were far from conclusive.¹⁰⁻¹² This article will show the basis for those cautions in detail by applying standard epidemiologic criteria to those data, and demonstrate the importance of such analyses in preventing premature implementation of mass screening technologies.

Accepted for publication March 7, 1991.

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BACKGROUND

Neuroblastoma is thought to be an embryonal tumor, present at birth and arising from cells in the sympathetic nervous system. Most tumors arise from the adrenal medulla and become clinically detectable as abdominal masses. Annual incidence in the United States based on Surveillance, Epidemiology, End Results (SEER) data for 1973 to 1982 was 8.5 per million children under age 15 years (95% confidence interval, 7.6 to 9.4 per million), with 85% of this incidence occurring before age 4 years, and 96% by age 9 years.¹³ Incidence rates from 6.6 to 10.6 per million children have been reported in other countries, with the age pattern being similar in all regions.

It has long been recognized that age and stage have strong, independent effects on prognosis, with survival exceeding 90% in young, early-stage infants and dropping below 20% in older, late-stage cases.^{14,15} This supports the notion that neuroblastoma is a congenital malignancy that grows from birth, and the longer before it is "caught," the worse the prognosis due to older age and/or more advanced stage. Neuroblastoma has at least one form that is known to spontaneously regress.^{16,17} One autopsy study found neuroblastomalike cells in 30% of newborns who died of other causes.¹⁸

Several discoveries during the past 7 years about the molecular biology of neuroblastoma showed that this simple conceptual model relating age, growth, spread, and prognosis was flawed. Brodeur et al¹⁹ reported in 1984 that amplification of the proto-oncogene *N-myc* had a very strong correlation with survival independent of stage and age. That same year, Look et al²⁰ reported that DNA ploidy had a strong relationship with prognosis, and this was confirmed in subsequent research.²¹⁻²⁷ Bourhis et al²⁸ found that once DNA ploidy and *N-myc* status were determined in a multivariate analysis of neuroblastoma prognosis, age no longer had an independent effect on prognosis. Most importantly, in addition to improving statistical prediction, such biologic markers have a potentially close link to basic mechanisms of oncogenesis.^{29,30}

These reports, along with succeeding confirmatory research, have led to the suggestion that neuroblastoma may include two types of disease. The first is a true congenital tumor that is growing at birth, probably slowly, and is of the good prognostic type, usually presenting at a young age as a mass, without extension or metastases. The second type may lie dormant until an activation step occurs at later ages, then growing quickly and aggressively, often having metastasized by the time the primary mass is detected.^{10,11}

The Japanese neuroblastoma screening program conducted urine tests on infants at age 6 months. Initially, only vanillylmandelic acid (VMA) levels were tested using a qualitative "spot test," based on a color change of treated paper.⁵ Later, some districts increased test sensitivity by adding a thin-layer chromatography test for homovanillic acid (HVA) levels.³¹ Most recently, some regions have used high-performance liquid chromatography (HPLC), the most sensitive of the three methods for testing levels of both VMA and HVA.^{32,33}

THE SCREENING DATA

The data from the original Japanese reports are summarized herein in the order in which they were published, to give some sense of how perceptions of neuroblastoma

screening were formed. The emphases in these summaries are not always those of the authors. The main focus in most of the articles from Japan was on the excellent outcomes of screened cases, and on the rates of false-negative and -positive test results, which were thought to represent the main "costs" incurred by the test. Here, the focus is on the observed incidence rates and prevalence of positive results among those screened. These are then compared with expected rates in the epidemiologic analysis that follows.

There have been many reports since 1984 on the Japanese screening experience, some of them overlapping; six of the most important are summarized in the Table. The first study was that by Sawada et al⁶ on screening experience in Kyoto from 1974 to 1979, using the spot test. They reported that the test identified four patients out of 78 331 infants screened at age 6 months (a prevalence of 1 in 19 500).

Two years later, Sawada et al³⁴ analyzed all patients treated at Kyoto University from 1962 to 1982. Stage, age, and survival were reported for 35 patients identified before screening started in 1974, and the 22 patients identified after that time. The proportion of patients identified at a young age or early stage was greater in the screened cohort than in the earlier unscreened one, and survival rates were much higher. However, 16 of the 22 patients from the screening period were detected clinically and not through the test, so the shift to diagnosis at earlier ages and stages was partially attributed to an indirect effect of screening: greater awareness among Kyoto pediatricians of the need for good abdominal examinations, with consequent increased clinical recognition. The number of cases annually was virtually constant throughout the entire period: 2.9 per year between 1962 and 1973 and 2.8 per year between 1974 and 1982. In a separate study, Sawada et al³⁵ reported that the Kyoto incidence rate, including the screened cases, was 13.3 cases per million person-years for children under age 15 years, and 93 cases per million person-years for infants under age 1 year.

The next major screening report was in 1984, the first from the MSSG.³⁶ The previously described Kyoto cohort made up 42% of the infants screened in this report. This study reported approximately the same prevalence of true positive results as had the Kyoto studies—16 in 281 939 cases, or about 1 per 18 000 infants. However, two regions that used modified testing procedures had very high prevalences (1 in 6 400 and 1 in 4 000), providing all but one of the cases found outside Kyoto.³⁷ As in the previous reports, screened cases had excellent prognoses. In 1986, an update by the MSSG added nine new cases, and showed a continued prevalence of 1 in 19 000 infants, with excellent outcomes.³⁸ In April 1985 the Japanese government recommended that all local governments develop mass screening programs.

The most influential study appeared in 1987, in which Nishi et al³⁹ reported on the Sapporo (Japan) screening program. The city of Sapporo commenced screening in 1981, but the surrounding prefecture of Hokkaido did not have a program. In both regions, pediatric cancer cases were reported to the same children's cancer registry that had been in place since 1969. Nishi et al compared neuroblastoma cases in the two regions before (1969-1980) and during (1981-1984) testing in Sapporo.

Figure 1, derived from the data of Nishi et al,³⁹ summarizes their most important result. Briefly, the age and

**Summary of Characteristics and Results of Main Published Japanese Reports
on Neuroblastoma Screening, 1982-1990***

Source, y	Source of Screened Population	Method of Detecting Unscreened or Missed Screened Cases	Source of Comparison Population	Type of Test	Size of Screened Population	No. of Cases/No. Screened/No. Missed at Clinical Presentation	Prevalance of True-Positives in Screened Population	Primary Outcomes
Sawada et al, ⁶ (1982)	11 Health centers in Kyoto, 1973-1979	Not stated	None	VMA Spot test	78 331	4/1/?	1/15 700	Good survival of screening-detected patients
Sawada et al, ³⁴ (1984)	8 Districts in Japan (MSSG), including Kyoto	Not stated	None	Several methods, mainly qualitative ³⁸	281 939	16/6/?	1/17 600	Favorable age/stage of screened cases, and good short-term survival
Sawada et al, ³⁶ (1984)	Kyoto, 1974-1982	Patients treated at Kyoto University	Kyoto, 1962-1974	VMA Spot test	117 103	6/1/16	1/16 700	Improvement of survival, age, and stage of 22 patients found in screening era (6 via screening) compared with prescreening era
Nishi et al, ³⁹ (1987)	Sapporo, 1981-1984	Pediatric tumor registry	Sapporo, 1969-1980; Hokkaido, 1969-1980, 1981-1984	Spot for VMA, TLC for HVA	73 226	11/4/1	1/4900	Dramatic favorable shift in age and stage distribution, with improved survival (20%-90%) comparing Sapporo before-after screening and concurrently with Hokkaido
Sawada et al, ⁴¹ (1988)	MSSG, 9 regions, 1981-1986	Unstated, different in each region	Case from JPSR, 1971-1976, and USCCSG	Several methods, mainly qualitative	Not stated	89/?/?	1/15 500-1/18 800	Good age/stage distribution and survival compared with USCCSG reports and JPSR; median tumor weight, 50g, 70% of abdominal neuroblastomas palpable after screening
Naito et al, ⁴³ (1990)	Sapporo and Hokkaido, 1981-1989 (Hokkaido started screen in 1987)	Patients undergoing surgery at two hospitals (? 60% of total)	Sapporo and Hokkaido, 1972-1980	1981-1984, Same as Nishi et al, ³⁹ 1984-1989, HPLC	Unknown	27/2/23	Unknown	Improvement in stage and resectability of screened tumors and improved 5-year survival of screening era cases, compared with cases in prescreening era (67% vs 23%)

*VMA indicates vanillylmandelic acid; MSSG, Mass Screening Study Group; TLC, thin-layer chromatography; HVA, homovanillic acid; JPSR, Japanese Pediatric Surgery Registry; USCCSG, US Children's Cancer Study Group; and HPLC, high-performance liquid chromatography.

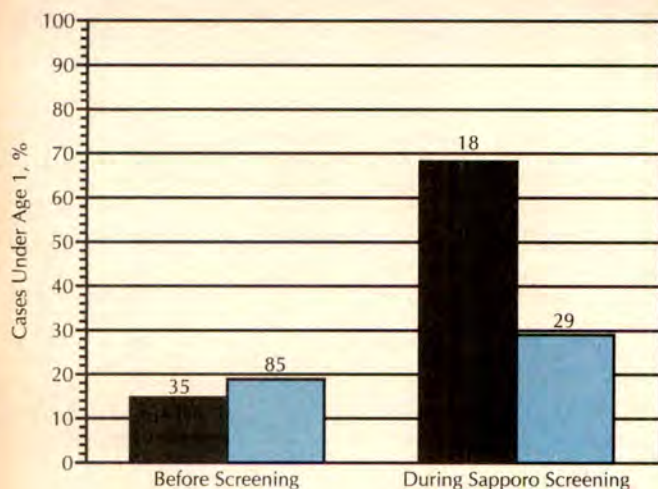


Fig 1.—Percentage of neuroblastoma cases in patients under age 1 year in Sapporo, Japan (solid bars), and Hokkaido, Japan (shaded bars), before screening was started (1969 to 1980) and during screening in Sapporo (1981 to 1984). Numbers above bars indicate the total number of cases. Based on data from Nishi et al.³⁹

stage distribution of cases was similar between Sapporo and Hokkaido in the years before screening, but after screening commenced in Sapporo, cases in that city showed a dramatic shift to younger ages and earlier stages. The long-term survival rate increased from 25% to 90% in Sapporo but was unchanged in Hokkaido. Eleven of the 18 cases in Sapporo in this latter period were identified through screening. Of 73 226 infants screened, 15 (1 per 4900) tested positive and had the disease. Four additional infants initially tested negative, but were diagnosed with neuroblastoma after age 6 months, for a total neuroblastoma risk of 1 per 3900 in this cohort.

Later in 1987, Sawada et al⁴⁰ reported that after the January 1985 shift to the more sensitive HPLC screening in Kyoto, the prevalence of positive results increased from 1 in 17 800 to 1 in 5000; however, the reason for the apparent increase was uncertain.

In 1988, a report by the MSSG on 89 screening-detected cases (which included the 25 previously reported cases) showed continued good outcomes. Prevalence among screened infants was 1 in 15 000 to 18 000. Of 80 patients with abdominal neuroblastoma, 70% had palpable masses, although 50% of the total had tumors that weighed less than 50 g.⁴¹

With the adoption of testing throughout Japan, the possibility of another natural experiment like that conducted by Nishi et al diminished. However, in 1989, they compared results from districts still using low-sensitivity detection methods with those from Sapporo, which had used the high-sensitivity HPLC since 1984.⁴² The screening prevalence was 1 in 5500 in Sapporo and 1 in 24 630 in the low-sensitivity districts. The median size of the tumors found in Sapporo was less than half of those in the other districts (24 vs 60 g); the median metabolite levels in Sapporo were half of those in the other regions; and the percentage of cases in stage I was double (40% vs 20%). They concluded, "... more patients with a small tumor must have been missed in the districts of qualitative methods."

In 1990, Naito et al⁴³ extended the 1987 data of Nishi et al³⁹ based on screening in Sapporo, and reported a dramatic improvement in surgical mortality and progn-

sis among screened cases in Sapporo and Hokkaido (where screening started in 1987) detected through March 1989. The 5-year survival rate improved from 23% in the prescreening era to 67% during screening, based on approximately 50 cases in each group. They concluded that while screening still had problems related to cost, false-negative results, and HVA/VMA cutoff values, "... this program is steadily improving the prognosis for neuroblastoma. Because of these results we suggest that the efforts to perfect and implement such programs elsewhere will similarly have a positive impact on outcome from neuroblastoma." Commenting on this article, a noted US pediatrician commented, "I cannot understand why screening for neuroblastoma in infants has not become routine in the US. ... I would suspect that there are other pilot studies which will eventually be reported. I would argue that there is no reason to wait."⁹

More recently, data from Sawada et al show a continuation of previous patterns. Of 337 cases detected by screening through 1988 by the MSSG, 58% had tumors of less than 50 g, and 52% of the 293 abdominal neuroblastomas were palpable. In Kyoto, the prevalence stayed as high through 1988 as it had been in the 1987 report, eight cases in 36 000 screened (1 in 4600). This corresponded with a shift to younger patients and increase of 5-year survival rate from 17% in the prescreening period to 55% and 85% during low-sensitivity and high-sensitivity screening, respectively (Tadashi Sawada, MD, personal communication, March 1990).

EPIDEMIOLOGIC ASSESSMENT

Did these reports provide strong evidence that screening could improve the prognosis for neuroblastoma? We will attempt to answer this by applying standard epidemiologic criteria to these data. The four basic epidemiologic biases that all studies of early disease detection or screening can be subject to are as follows: referral bias, detection bias, lead-time bias, and length-time bias.^{44,45} Each one will be discussed in relation to the neuroblastoma screening data.

Referral (Selection) Bias

This bias is produced when the screened population is self-selected or chosen by the investigator so that their prognosis, once the disease is recognized, is better than that of the unscreened population. It is evaluated by examining the process and outcome of screening selection. There should be no known prognostic factors that are unbalanced between the screened and unscreened populations. No strong demographic or environmental risk factors for neuroblastoma have yet been identified,¹³ nor are any such factors (aside from age) known to be associated with prognosis. Thus it is unlikely that the screened populations could self-select to have either different neuroblastoma risk than the unscreened group or a better prognosis once disease was identified.

Detection (Overdiagnosis) Bias

This bias occurs when screening detects disease that would never have presented clinically, ie, it would have spontaneously regressed and never been noticed if not for the test.

The only way to definitively assess overdiagnosis is by comparing age-specific and overall disease incidence rates between screened and unscreened populations or before

and after screening in the same population. An incidence rate is the ratio of new cases to the number at risk during a specific time interval. Unfortunately, the number at risk is often difficult to define, and in none of the screening reports except that by Sawada et al³⁵ were incidence rates determined on a combined screened and unscreened population.

However, two indexes from these reports can be used as crude surrogates for incidence rates. The first is the annual number of cases in a defined geographic region. To draw any conclusions from such numbers, it has to be assumed that the population at risk is constant, and the reporting mechanisms are reliable and unbiased. If these conditions apply, the annual number of cases should be proportional to the annual incidence rate.

The second index is the prevalence of screening-detected disease among all those tested. Its relationship to incidence rates is not simple. Presumably, a screening-detected case is one that would have presented at a later age if the patient had not been screened. Therefore, with perfect screening, the proportion of infants in whom the disease is detected at the time of screening (prevalence of disease in the screened cohort) should be equal to the proportion of the cohort that would eventually have presented clinically at later ages (cumulative risk of disease beyond the screening age). If more cases are detected through screening than we would expect to detect clinically at and beyond the screening age, overdiagnosis is a likely explanation.

The subsequent analysis will show that both of those surrogate measures suggest that more infants were diagnosed with high-sensitivity screening than would have developed the disease later, making it possible that a certain proportion of them would have naturally regressed.

Screening Prevalence.—Sawada et al³⁵ reported in 1984 that the incidence rate in Japan for children under age 15 years was 8.2 per million per year. This is equivalent to a total neuroblastoma risk for the first 15 years of life of about $15 \times 8.2 \times 10^{-6}$, or 1 in 8130. Since about 25% of all cases occur before the screening age of 6 months, the prevalence of cases at the time of screening should be about $0.75 \times (1/8130)$, or 1 in 10 840. If the test had a sensitivity of 75%, we should have expected the Japanese researchers to find neuroblastoma in approximately 1 per 14 000 infants tested.

The earliest reports were consistent with these numbers, showing a prevalence of 1 in 15 000 to 18 000 among screened infants, using the qualitative VMA spot test, with a sensitivity of about 75%.^{39,46} However, the addition of more sensitive testing methods increased the prevalence of positive results to 1 in 5000 in both Sapporo and Kyoto, suggesting that the number of cases diagnosed with those techniques might have been twofold to threefold higher than would have presented clinically without screening. The prevalence based on the total Japanese screening experience has so far not appeared excessive, because cumulative reports have included the early qualitatively tested populations, and many prefectures still use low-sensitivity tests.⁴¹

Number of Cases per Year.—Several years of screening should result in an increase in the number of cases diagnosed before age 1 year by exactly the same amount as the decrease in the number diagnosed after that age. If the test overdiagnoses tumors, the increased number of cases in the first year of life will be greater than the reduction at

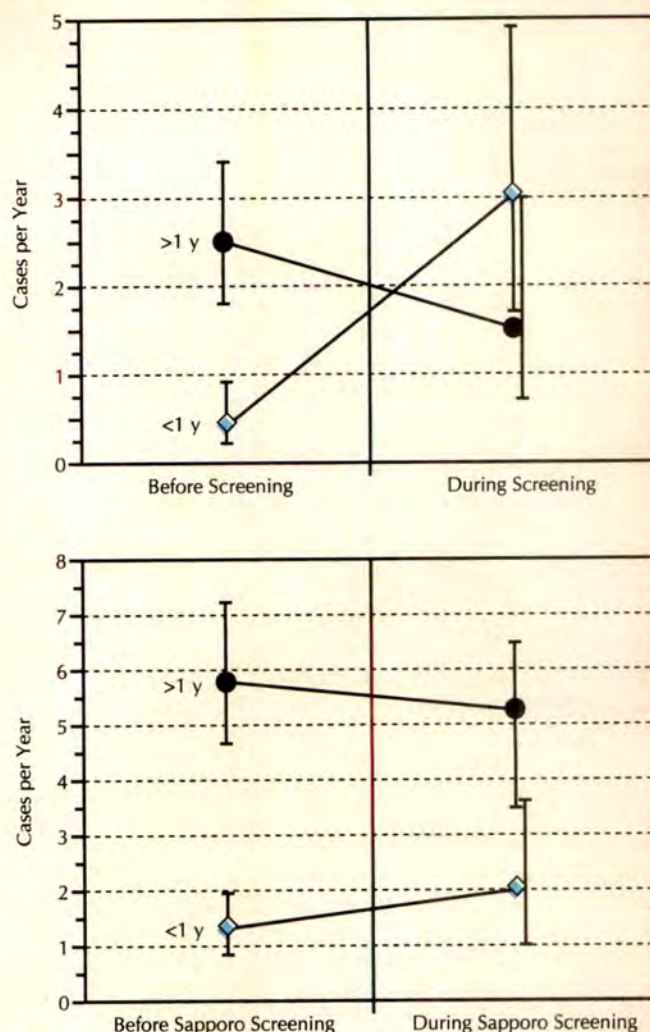


Fig 2.—Annual number of neuroblastoma cases, by age, in Sapporo (top) and Hokkaido (bottom) during the years before screening (1969 to 1980) and during screening in Sapporo (1981 to 1984). Error bars represent 95% confidence intervals. Based on data from Nishi et al.³⁹

older ages.

This shift to younger ages is what Nishi et al³⁹ claimed to have demonstrated in 1987 (Fig 1). Figure 2 redisplayes the numbers from Fig 1, presented now as annual number of cases, with 95% confidence intervals. This figure shows that an interpretation different from that in the original article was also supported by these data. Looking first at data from Hokkaido, where there was no screening, we see a minimal, nonsignificant change in the annual number of cases in both age categories before and during the Sapporo screening periods. In Sapporo, where the prevalence of positive results was high, the pattern was quite different. Among children over age 1 year, there was a statistically nonsignificant decrease of about 1 case per year after the onset of screening. Among those under age 1 year, there was a statistically significant increase of 2.5 cases per year, a sevenfold change. There was only minimal statistical evidence that the rate in older children had changed, and even if change were real, it was less than the statistically significant increase among the younger children.

Thus, we find that in a study with probably good case ascertainment (through a single tumor registry), sensitive

screening method, and use of two comparison groups (historical and concurrent), the data suggested that the elevation in the number of cases among children of screening age was larger than the reduction in incidence at older ages. This shows that case totals can be deceptive when overdiagnosis is a possibility. However, a definitive interpretation of these data is not possible due to the lack of denominators and the fact that screening was performed for too short a time (4 years) for the effect of screening to be apparent in the older ages.

In the early reports by Sawada et al³⁴ from Kyoto, the number of annual cases diagnosed when the VMA qualitative test was used (1974 to 1982) was not different from that in the years before screening was started. However, more recent data from the era of high-sensitivity testing in Kyoto show a pattern almost identical to that of the Sapporo data of Nishi et al. The annual number of cases under age 1 year increased from 0.6 in the prescreening years (1962 to 1974) to 3.2 in the period when HPLC testing was used (1983 to 1988). In the same periods, the annual number between ages 1 and 2 years was unchanged, and above age 2 years it dropped from two to one case annually (T.S., personal communication, March 1990).

Size of Detected Tumors.—The data of Sawada et al and Nishi et al on the size of screening-detected tumors are consistent with the twofold to threefold overdiagnosis suggested by the previous numbers. Virtually all patients (96%) are asymptomatic at the time of screening, and when HPLC is used, 75% of screening detected abdominal tumors weigh less than 50 g.⁴² Even with knowledge of the screening status, only half of screening-detected abdominal tumors are palpable. The yield of HPLC testing is thus at least twice that clinically detectable at the time of screening. Clinical detectability is not known to predict progression, but it is interesting that the proportion of possible "overdiagnosed" cases suggested by the prevalence and annual numbers of cases is similar to the proportion of clinically undetectable ones.

A finding of overdiagnosis does not eliminate the possibility that a screening program might be of benefit if it can be determined that the prognosis of nonoverdiagnosed cases is improved by earlier detection. However, overdiagnosis injects another serious cost (ie, unnecessary treatment of overdiagnosed cases) into the cost-benefit equation.

Lead-Time Bias

This bias exists when the survival of the screened patients from the time of diagnosis appears longer only because their conditions were diagnosed earlier; they still die at the same age they would have without the early diagnosis.

The purpose of screening is to either reduce overall mortality rates or shift the age-specific mortality to older ages. If there is lead-time bias, age-specific mortality rates will remain constant even though survival time after diagnosis appears longer. Lead-time bias "slides" survival curves over, ie, they show the same long-term survival, but with a longer period of low mortality at the beginning.

In both the before-after comparisons of Sawada et al and the parallel comparisons of Nishi et al, long-term survival was substantially better in screened cases than in those detected clinically (approximately 90% vs 20% to 30%), a difference that cannot be produced by lead-time bias. The 55% 5-year survival rate of the Kyoto cases during the qualitative screening period (1974 to 1982) was

better than the 20% survival rate before screening, but it was comparable with the survival rates from the United States and Denmark at that time,^{3,11,47} suggesting a contribution of improved medical care. However, medical care could not explain the concurrent Sapporo-Hokkaido comparison, in which all cases were treated in the same hospital at the same time. However, the survival curve approach cannot be used in the presence of overdiagnosis, since this will "pad" the screened cases with patients with good prognoses who would not have been included in these curves without the screen, making it appear as though something more than a time-shift has occurred. In such a situation, only age-specific mortality rates can be used, which were not reported.

Length-Time Bias

This effect occurs if the timing of screening in some way selects for cases with better prognoses. It derives its name from the situation in which a test preferentially picks up patients with slower-growing tumors with the longest preclinical detection phase, because faster-growing disease will be more likely to have been clinically recognized before screening.

This is a difficult bias to assess because the good outcome of the screening-detected tumors is usually ascribed to early detection and not to the selection of less aggressive cases. Its presence is strongly suggested when, even after controlling for other biases, screening-detected cases appear to do well without a concomitant change in age-specific mortality rates. If screening is repeated periodically, such as with Papanicolaou smears and mammograms, this effect diminishes and the outcome of initial and later screens can be compared. Alternatively, if there is any intrinsic biologic marker of disease aggressiveness, this can be used to evaluate whether screening-detected cases are qualitatively different from those later detected with symptoms.

With the finding of N-myc amplification and diploidy as strong negative prognostic factors, neuroblastoma is one of the unusual diseases in which this bias can be directly assessed. It is known that there is a strong association between young age and good prognostic markers among those that present clinically.^{28-30,48} If screening detected tumors that would have presented at older ages, we would expect the proportion of screening-detected cases with bad prognostic markers to be higher than among those that clinically present at the same age. If a length-bias or similar effect were operating, another pattern would appear: screened cases would have the same fraction of favorable prognostic markers (or higher, if there is overdiagnosis) than those that present clinically at the same age.

This latter pattern is what has been shown clearly among the screened cases studied so far. There have been several studies comparing genetic markers among screening-detected cases, clinically detected cases under age 1 year, and those that presented clinically at older ages.^{21,49-51} All of the studies show that both screening-detected cases and young clinical cases have a high percentage of good prognostic markers, and no screening case has yet been reported with N-myc amplification. These patients have had excellent survival. In contrast, those who presented clinically at older ages have had very poor prognostic markers and their long-term survival has been correspondingly poor. The

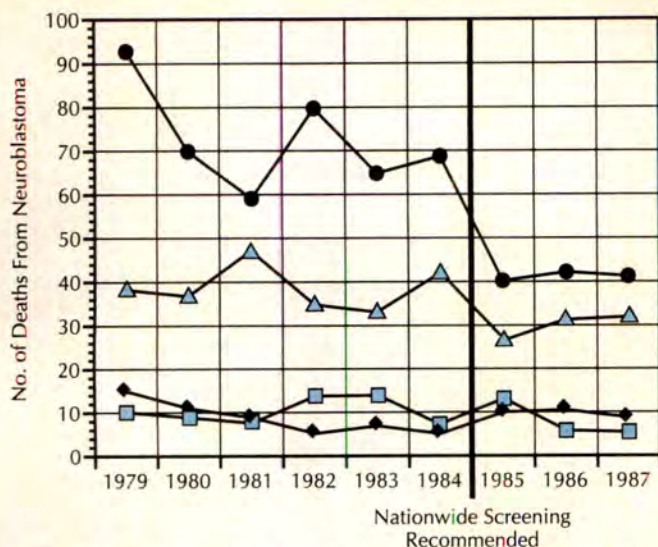


Fig 3.—Annual number of deaths from neuroblastoma according to death certificates issued by the Japanese Ministry of Law between 1979 and 1987. Screening started in individual districts before 1985, and is being phased in nationally since then (see text). Squares represent newborns; circles, children between ages 1 and 4 years; triangles, children between ages 5 and 9 years; and diamonds, children less than age 10 years.

authors of the largest study of this type concluded that screening at age 6 months missed most of the poor prognosis neuroblastomas.⁵¹

This evidence suggests that many of the screening detected cases are not ones that in the absence of screening would later become poor prognostic cases. If true, this would weaken the primary rationale for screening. However, if an untreated tumor of good prognostic genotype could evolve into one of poor prognostic genotype, the observed patterns would not be evidence that screening was missing poor prognosis tumors. Brodeur et al⁵² addressed the question by following up 60 patients being treated for neuroblastoma, and found none whose *N-myc* amplification changed with relapse or progression, even under the selective pressure of chemotherapy. This is further support for the contention that the known age/stage pattern of prognosis and disease may be the manifestation of the two distinctly different biologic processes.

Whatever biases may be operating, the final, definitive measure of the benefit of screening is the difference in age-specific mortality rates between screened and unscreened populations, preferably compared concurrently. As yet, no such data have been reported from Japan or elsewhere, although the Canadian project will provide such numbers.⁷ The data of Dr Tadashi Sawada (personal communication, March 1990) on the number of deaths from neuroblastoma reported in Japan through 1987 are the only related numbers available at this time (Fig 3). The sudden decrease in the number of cases in the 1- to 4-year age group in 1985 is both intriguing and puzzling. It is difficult to attribute this entirely to mass screening, since it was recommended but not immediately instituted nationwide in 1985. Screening was performed in a number of districts before that time; however, it takes at least 3½ years for the effect of screening at 6 months to be fully apparent in a 1- to 4-year age group. Since neither a denominator nor completeness of the reporting mechanism

is known, it is not possible to know at this time what this pattern represents, or if it will continue.

CONCLUSION

The Japanese neuroblastoma screening studies were an ambitious and exciting attempt to examine the potential of a new technology to reduce mortality from an often fatal pediatric disease. However, the application of rigorous epidemiologic criteria to the Japanese neuroblastoma screening data might have tempered early enthusiasm. As has occurred in the United States for other childhood diseases,⁵³ this enthusiasm resulted in pressure to institute neuroblastoma screening programs. A formal epidemiologic analysis would have drawn attention away from false-negative and false-positive rates and the survival of detected cases, and instead highlighted the importance of missing data (incidence and mortality rates) that are critical to the evaluation of biases that can produce an illusion of screening benefit. It would have raised the possibility of twofold to threefold overdiagnosis, and could have suggested the presence of a length-time effect. In the absence of mortality rates, recent studies based on genetic prognostic markers have provided strong evidence that high-sensitivity screening preferentially detects cases that would have had excellent prognoses even if they had later presented clinically. At this time, there are few data on the effect of advancing the time of diagnosis within biologic prognostic categories, so the effect of using different, or multiple, screening ages is not known. The status of neuroblastoma screening is very uncertain at this time, and further data from Japan, as well as Canada, are needed to determine whether screening is harmful or beneficial, and at what individual and societal cost.

This work was supported in part by grants from the Maryland Children's Cancer Foundation, Baltimore, and the CSX Corporation, Baltimore.

We thank Tadashi Sawada, MD, for graciously supplying Japanese screening data through 1988 and granting permission for its use.

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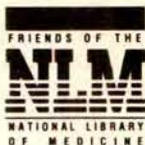
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Value of Subject Height in Predicting Lower Esophageal Sphincter Location

Annamaria Staiano, MD, Ray E. Clouse, MD

● Subject height and lower esophageal sphincter location were determined in 213 children and adults to determine whether the anthropometric variable could be used to accurately predict sphincter location across all age ranges. The upper margin of the lower esophageal sphincter was determined with a nasally placed manometry catheter. Height was highly predictive of lower esophageal sphincter location across all subject groups ($r^2 = .96$) and in the youngest subset of subjects (≤ 2 years of age, $r^2 = .88$). The predictive ability of height remained significant but progressively decreased in the four older subject groups (>2 and ≤ 10 years of age, $r^2 = .74$; >10 and ≤ 20 years of age, $r^2 = .66$; >20 and ≤ 40 years, $r^2 = .58$; and >40 years, $r^2 = .49$). The regression equation that described subjects 2 years of age or younger ($L = 0.22[H] + 4.92$, where L is the location in centimeters from the nares and H is the height in centimeters) correctly predicted lower esophageal sphincter location within 1.0 cm in 90% of these subjects. In the older subject groups, predicted lower esophageal sphincter location was in error by greater than 2 cm in 25% to 35% of the subjects, even when age group-specific regression equations were used. Decreased predictive ability related to both increasing age and increasing height. We conclude that lower esophageal sphincter location can be predicted from height in subjects up to 2 years of age. The prediction is sufficiently accurate in this age group to allow placement of pH probes without manometric measurements.

(AJDC. 1991;145:1424-1427)

Prolonged intraesophageal pH monitoring is being increasingly used in children and adults to diagnose and treat gastroesophageal reflux disease.^{1,2} Proper placement of the pH probe in relation to the lower esophageal sphincter (LES) is essential for correct interpretation of the study results. Manometry has become the established standard for determination of the proximal margin of the LES, but this procedure can add considerable expense and patient discomfort if manometric studies are not otherwise required. In 1979, Strobel and colleagues³ demon-

strated that esophageal length correlates well with subject height in children. To our knowledge, this observation has not been reproduced, the accuracy of such a correlation in relation to age groups is unknown, and the use of a calculation based on height is rarely employed despite its potential advantages. Herein, we examine the relationship of subject height to LES location (manometric determination) in groups of patients ranging from younger than 2 to older than 40 years to determine the potential value of this measurement for the placement of intraluminal pH probes.

SUBJECTS AND METHODS

Manometric tracings and clinical records from the University of Naples (Italy) and Washington University School of Medicine, St Louis, Mo, were reviewed to identify subjects for this study. Consecutive subjects who had been referred for evaluation of esophageal symptoms or symptoms potentially indicative of gastroesophageal reflux from 1987 through 1990 were included until at least 20 subjects collectively in each of five age groups were found (age ≤ 2 years, age >2 years and ≤ 10 years, age >10 years and ≤ 20 years, age >20 years and ≤ 40 years, and age >40 years). Patients who had undergone manometry but in whom the LES had not been traversed were excluded, as were neurologically impaired children and other subjects in whom accurate height measurements could not be obtained.

Esophageal manometry was performed similarly at the two institutions according to previously reported methods.^{4,5} A transnasal triple-lumen manometry catheter with a 2.4-mm outside diameter was used for children younger than 10 years, and a catheter assembly with a 3.8-mm outside diameter was used for older subjects. Recording ports were spaced at 2- and 5-cm intervals along the smaller- and larger-diameter catheters, respectively. The manometry catheters were perfused with a low-compliance pneumohydraulic perfusion device. In subjects of all ages, the proximal margin of the LES was determined as the highest position recording from a high-pressure zone as the catheter was withdrawn in a stepwise fashion (0.5-cm steps in children younger than 15 years; 1.0-cm steps in all other subjects). Location was averaged from all three lumina, and this position was recorded in centimeters from the nares. The length in infants (subjects younger than 2 years) was measured by two observers with the child in the supine position on a board with a vertical support for the head and an adjustable vertical support for the feet. For the purpose of consistency, infant length will be referred to herein as height. Heights in older subjects were measured with a movable anthropometer while standing without shoes. Height measurements were compared with published population standards for children and adults.^{6,7}

Accepted for publication May 13, 1991.

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Table 1.—Clinical Characteristics of the Subjects

Age Group, y	No.	Gender M/F	Median Age, y (Range)	Median Height, cm (Range)
≤2	72	46/26	0.5 (0.1-1.7)	63 (52-94)
>2-≤10	31	22/9	5.2 (2.2-9.2)	107 (76-135)
>10-≤20	20	12/8	13.0 (10.5-20.0)	155.5 (118-182)
>20-≤40	32	13/19	34.0 (21.0-40.0)	169.5 (152-188)
>40	58	22/36	57.5 (41.1-89.0)	168 (152-191)

Herein, grouped data are presented as the median and range. Linear regression equations were determined for predicting LES location from subject height, and the coefficient of determination (r^2), reflecting the overall variation of one variable (height) in relation to another (LES location), was calculated to compare the relationships for each age group. Significance levels less than .05 were required.

RESULTS

A total of 213 subjects were included in the study. Characteristics of the subjects in each of the five age groups are shown in Table 1. The third group (>10 and ≤20 years) contained the fewest subjects, because indications for manometry or pH monitoring are infrequent in this age subset. On average, each group fell within 15 percentiles of the general population means of height for age (median percentile for each group: ≤2 years, 36th percentile; >2 to ≤10 years, 36th percentile; >10 to ≤20 years, 39th percentile; >20 to ≤40 years, 51st percentile; and >40 years, 40th percentile).

The scatter diagram and regression line showing the relationship of LES location to height for all subjects is shown in Fig 1. It is apparent from this figure that the relationship is better for younger subjects of lesser height than for the older subjects of greater height. Separate regression equations predicting LES location from height were calculated for each age group (Table 2). All r^2 values derived from these equations were highly significant ($P<.001$ for each), but the prediction deteriorated with increasing age. Actual LES locations were compared with predicted locations for the subjects in each group to determine the accuracy of the estimate in this reference population (Table 3). For the youngest group, predicted LES location was within 1 cm of the actual LES location in more than 90% of cases and was within 1.5 cm in all subjects. In contrast, predicted LES location fell within 2 cm of the actual LES location in only 64.5% to 74.1% of subjects in the four older age groups. Ninety percent or more of subjects were included in the groups between 2 and 40 years of age, only if a variation of 3 cm or less was permitted. Because the clinical utility of the equations to predict LES location from height appeared to be restricted to the youngest age group, a separate scatterplot with the regression line and 95% confidence intervals is shown for this group in Fig 2.

Regression equations were also calculated separately for male and female subjects within each age group. The relationship between height and LES location remained significant for both male and female subjects when all subjects and the two subgroups aged 10 years or younger were considered (all subjects: $r^2 = .96$ for each gender; age ≤2 years: $r^2 = .86$ for female subjects, $r^2 = .88$ for male subjects; age >2 and ≤10 years: $r^2 = .74$ for each gender; $P<.001$ for each). In the three older age groups, the relationship

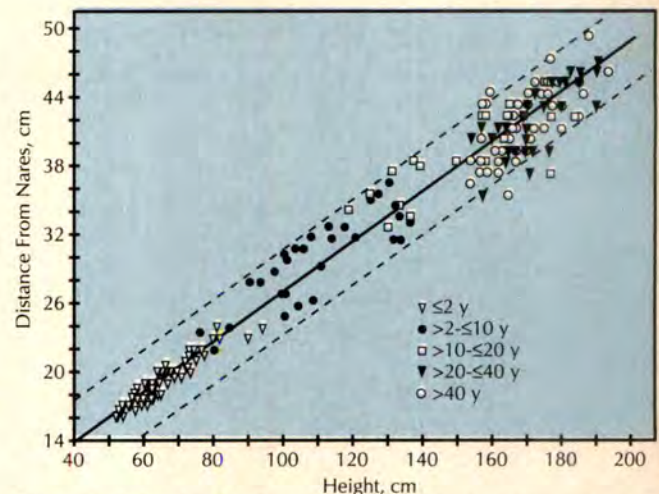


Fig 1.—Relationship between subject height and distance to the lower esophageal sphincter from the nares, as determined with manometry. The dashed lines outline the 95% confidence band for predicting lower esophageal sphincter location at any specific height ($r = .98$).

Table 2.—Regression Equations for Predicting Lower Esophageal Sphincter Location* From Subject Height

Age Group, y	Regression Equation†	r^2 ‡	SE of the Estimate
≤2	$L = 0.22(H) + 4.92$.88	0.71
>2-≤10	$L = 0.20(H) + 8.53$.74	2.26
>10-≤20	$L = 0.16(H) + 15.61$.66	2.49
>20-≤40	$L = 0.23(H) + 3.93$.58	2.05
>40	$L = 0.24(H) + 2.98$.49	2.22
All subjects	$L = 0.23(H) + 4.71$.96	1.91

*Location of lower esophageal sphincter was measured as the distance to the lower esophageal sphincter in centimeters from the nares.

†L indicates lower esophageal sphincter location in centimeters from the nares; H, subject height in centimeters.

‡ $P<.001$ for each.

relationship appeared to be stronger for female subjects than for male subjects (age >10 and ≤20 years: $r^2 = .81$ for female subjects and $r^2 = .62$ for male subjects; age >20 and ≤40 years: $r^2 = .62$ for female subjects and $r^2 = .52$ for male subjects; age >40 years: $r^2 = .61$ for female subjects and $r^2 = .23$ for male subjects), although r^2 values were significantly different from zero within each subgroup ($P<.05$ for each).

COMMENT

These data demonstrate the striking accuracy with which height is predictive of LES location (determined as

Table 3.—Precision of the Regression Equations in Predicting Lower Esophageal Sphincter Location* When Applied to the Study Subjects

Age Group, y	Difference in Predicted and Measured Locations, No. (%)			
	≤1 cm	≤1.5 cm†	≤2 cm	≤3 cm
≤2	65 (90)	72 (100)	72 (100)	72 (100)
>2-≤10	9 (31)	15 (48)	20 (65)	28 (90)
>10-≤20	6 (30)	...	13 (65)	19 (95)
>20-≤40	9 (28)	...	21 (66)	29 (91)
>40	23 (40)	...	43 (74)	51 (88)

*Location of lower esophageal sphincter was measured as the distance to the lower esophageal sphincter in centimeters from the nares.

†The 0.5-cm measurements were performed only in the first two age groups.

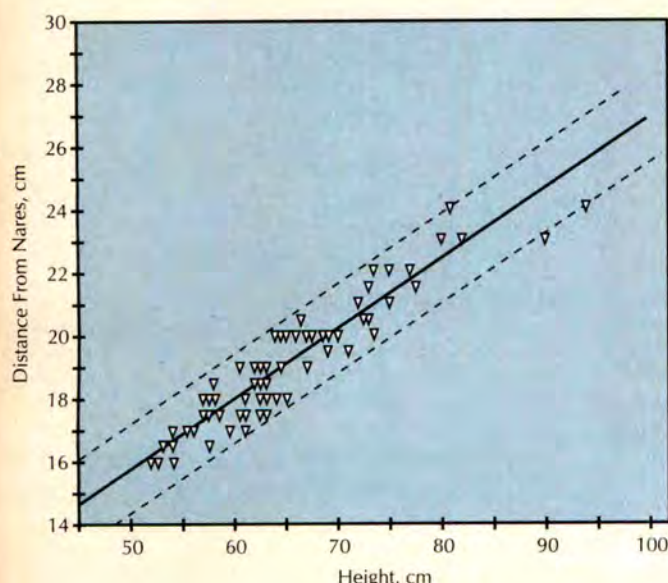


Fig 2.—Scatterplot and regression equation predicting lower esophageal sphincter location (L) (distance from nares) from subject height (H) (or length) in the youngest subject group (age ≤2 years). The equation $L = 0.22(H) + 4.92$ was used to form the solid line. The dashed lines outline the 95% confidence band for predicting lower esophageal sphincter location at any specific height.

the distance to the LES from the nares) across all age groups. However, the precision decreases as subject height increases, even during childhood, and significantly deteriorates in adults. This observation is particularly true for male subjects. A single regression equation ($L = 0.22[H] + 4.92$) describing the relationship of height (H) and LES location (L) in subjects aged 2 years or younger will accurately identify the location of the LES within 1.0 cm in more than 90% of subjects. A similar accuracy is not found in older subjects, even when regression equations defined solely by the age category are used.

Strobel and coworkers³ first examined this important relationship in children undergoing evaluation for suspected gastroesophageal reflux (all subjects <20 years). Earlier reports described an association of esophageal length with age,^{8,9} but the association was found to be more directly related to subject height than age, an inter-related variable. The regression equation $L = 0.252(H) + 5$

was derived by Strobel et al to determine the location of the LES with a transnasal catheter. Strobel et al suggested that a calculation of LES location could obviate the need for manometry before pH probe placement for the Tuttle test, a then-popular test for the diagnosis of gastroesophageal reflux in children.

Prolonged intraluminal pH monitoring is becoming an important tool for diagnosis and management of gastroesophageal reflux and its complications in all age groups. Fluoroscopy, manometry, and pH step-up on probe withdrawal into the esophagus have been utilized to appropriately identify the location of the LES. Although the last of these techniques could be most easily utilized with no additional equipment or morbidity, the technique is not sufficiently accurate to be used with confidence.¹⁰ Manometry (in children and adults) and fluoroscopy (in children) are now routinely employed.^{1,11-13} Since publication of the report by Strobel et al,³ many studies of intraluminal pH recording in children have been published, but the method of LES localization based on subject height has rarely been utilized in research reports, and only then has been utilized in conjunction with fluoroscopy.^{14,15} We suspect that this is related to several factors, including (1) the lack of data reproducing the original findings, (2) the fact that transoral catheters were used for the youngest children and that these measurements were used in calculating the regression equations, and (3) underrecognition of the method. A recent review suggests that the calculation of LES location for pH probe placement is beginning to gain some acceptance in clinical practice.¹⁶

Herein, we have expanded on the original observations in children and have explored the relationship between height and LES location in adults. Only transnasal manometry catheters were employed, and the most proximal region rather than the midpoint of the LES was determined; these methods are more applicable to pH probe positioning for prolonged monitoring. Thus, our regression equations could be considered more applicable by other investigators and clinicians, although they have not yet been applied prospectively to confirm validity. We derived a very similar equation for young subjects to that of Strobel and colleagues,³ a finding that would support the reproducibility of this method. Placement of a manometry probe simply to locate the LES before pH monitoring is particularly undesirable in the youngest subject group, as the manometry studies provide little additional information in this subset of subjects. The error in LES location with use of the regression equation is sufficiently small in children aged 2 years or younger to strongly advocate the use of calculated esophageal lengths as a standard method to determine probe placement. Gastroesophageal reflux and the need for 24-hour pH monitoring are also particularly important in these young children.^{1,14,17,18}

We were unable to show that height remained a good predictor of LES location with advancing age. Although data are not specifically provided, the relationship between height and LES location was poorer even in the younger and older subsets of the 2- to 10-year age group, as suggested by Fig 1. Deterioration of the relationship in adults could be explained by the occurrence of hiatal hernia or a shortened esophagus from esophagitis that would be expected to increase with age. However, such disorders would bias the relationship toward decreasing esophageal length with age, and no such bias was

observed (Fig 1). As worsening predictive precision appeared even in the older children and adolescents, it seems more likely that the relationship between visceral and skeletal growth only remains strong in infancy and early childhood. Considering that pH probes are placed 3 to 5 cm above the LES in children and adults (87% of the length from the nares to the LES in children and 5 cm above the LES in adults), placement error should be less than 2 cm, even in older subjects. Prospective evaluation of 24-hour pH monitoring results with the use of calculated vs measured LES location would actually be necessary to determine the adequacy of the simpler technique. The error in estimated LES location in the subjects older than 2 years, however, was unfortunately sufficient that this technique cannot be recommended at present for pH probe placement in any but the youngest patients, unless no other method is available.

The authors thank Maria Rosaria Andreotti, MD, and Mary Fahy, LPN, for performing the motility studies and Debbie Smith, PhD, Division of Biostatistics, Washington University School of Medicine, St Louis, Mo, for her assistance with the statistical analyses.

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Trimethoprim-Sulfamethoxazole Oral Desensitization in Hemophiliacs Infected With Human Immunodeficiency Virus With a History of Hypersensitivity Reactions

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● Hemophiliacs infected with human immunodeficiency virus with a history of hypersensitivity reaction to a combination product of trimethoprim and sulfamethoxazole were desensitized orally. Six of the seven patients included in the study successfully completed the desensitization protocol and received trimethoprim-sulfamethoxazole for 5 to 7 months after desensitization (mean length of treatment, 5.7 months) for prophylaxis of *Pneumocystis carinii* pneumonia. The small number of patients and the short follow-up allow us to suggest that oral desensitization may be an effective and inexpensive means to treat hemophiliacs infected with human immunodeficiency virus with trimethoprim-sulfamethoxazole as prophylaxis against *Pneumocystis carinii* pneumonia. (AJDC. 1991;145:1428-1429)

All patients infected with human immunodeficiency virus (HIV) with CD4 cell counts of less than $0.20 \times 10^9/L$ are at risk of developing *Pneumocystis carinii* pneumonia (PCP).¹ Major efforts have been made to prevent this infection. Several methods have been tried, including the use of a combination product of trimethoprim and sulfamethoxazole, aerosolized pentamidine, dapsone-trimethoprim, intravenous pentamidine,² and others. Patients with HIV infection have an increased frequency of hypersensitivity reactions to several drugs, including trimethoprim-sulfamethoxazole.^{3,4} The possibility of oral desensitization with trimethoprim-sulfamethoxazole prompted the study in HIV-infected patients with clotting disorders.

PATIENTS AND METHODS

Patients with clotting disorders followed up at the Arkansas Hemophilia Center, Little Rock, who had a history of hypersensitivity to trimethoprim-sulfamethoxazole were included in the study. All developed hypersensitivity reactions to trimethoprim-sulfamethoxazole ranging from erythema multiforme to minor respiratory difficulty and edema. Informed consent was obtained from seven patients, six of whom were male. The age range was 7 to 33 years, with a mean age of 19.3 years. The six males all had severe factor VIII deficiency, and the female had type III von Willebrand's disease. All patients were HIV positive and their CD4 cell counts were less than $0.2 \times 10^9/L$ when they were included in this study. The Table shows the clinical characteristics of these patients. Patients who had a history of exfoliative dermatitis or Stevens-Johnson syndrome were not included in this trial.

All patients were hospitalized at the time this procedure was at-

tempted. We used a regimen modified from that suggested by Yango and colleagues.⁵ Pediatric suspension of trimethoprim-sulfamethoxazole (Bactrim) was administered orally every 8 hours beginning with 1/10 000 of the desired total daily dose and progressing through serial dilutions of 1/5000, 1/1000, 1/500, 1/100, 1/50, and 1/10. Subsequently, the desired dosage was administered orally twice per day. If mild skin rashes developed, the patients were treated with antihistamines. The procedure was terminated with the development of systemic symptoms or exanthems involving the mucous membranes. Epinephrine and resuscitative equipment were kept readily available.

RESULTS

Five patients tolerated the procedure well without complications. Of the two remaining patients, one (patient 6) developed an erythematous rash that responded well to antihistamine therapy. Patient 1 developed an urticarial rash that responded partially to antihistamine therapy; the protocol was stopped inadvertently, but was subsequently restarted and completed successfully. All patients except patient 3 continued to receive trimethoprim-sulfamethoxazole for 5 to 7 months after desensitization; the mean length of treatment was 5.7 months. The patient who discontinued trimethoprim-sulfamethoxazole treatment had poorly complied with the dosage regimen and thus missed several doses. He then developed an urticarial rash, forcing the discontinuation of the drug, and was treated with aerosolized pentamidine. A second attempt to desensitize this patient failed due to the development of urticaria.

COMMENT

Trimethoprim-sulfamethoxazole is an effective and inexpensive means of preventing PCP. In a randomized study, patients with Kaposi's sarcoma and no history of opportunistic infections were assigned to receive trimethoprim-sulfamethoxazole vs placebo. None of the patients in the trimethoprim-sulfamethoxazole group developed PCP, while 16 (53%) of 30 patients in the control group developed PCP. Fifteen (50%) of the 30 patients in the trimethoprim-sulfamethoxazole group developed adverse reactions, including nausea, vomiting, pruritus, erythroderma, fever, and leukopenia.³

Recent studies have documented that the frequency of allergic reactions to drugs is increased in patients with HIV infection despite the compromise of their immune status.^{5,6} Because trimethoprim-sulfamethoxazole is one of the drugs of choice for prophylaxis and treatment of PCP, development of a safe and effective protocol for desensitization is of prime clinical importance.

Sullivan et al⁷ has shown that oral desensitization to penicillin is effective and relatively safe. Further evidence of successful oral desensitization to trimethoprim-sulfamethoxa-

Accepted for publication July 8, 1991.

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Clinical Characteristics of Patients Infected With HIV With Clotting Disorders Who Develop Hypersensitivity Reactions to Trimethoprim-Sulfamethoxazole*

Patient No./ Age, y/Sex	Factor Deficient	Absolute CD4 Count, × 10 ⁹ /L	CD4/CD8 Ratio	Type of Reaction	Other Medications at the Time of Reaction
1/7/M	VIII severe	0.021	0.05	Rash	Zidovudine
2/24/M	VIII severe	0.019	0.2	Rash	Zidovudine
3/15/M	VIII severe	0.049	0.2	Rash	Zidovudine
4/33/M	VIII severe	0.023	0.05	Rash	Zidovudine
5/15/M	VIII severe	0.017	0.05	Rash, dyspnea	Zidovudine
6/15/M	VIII severe	0.079	0.08	Rash, swelling	Zidovudine, tetracycline
7/21/F	VWD/III	0.199	0.5	Rash	Zidovudine

*HIV indicates human immunodeficiency virus; and VWD, von Willebrand's disease.

zole with subsequent intravenous administration of the drug was described by Finegold.⁸ Several investigators have successfully reported oral desensitization to sulfasalazine.^{9,10} Based on previous work, this approach is appealing since oral administration of trimethoprim-sulfamethoxazole is less likely to provoke a systemic reaction than parenteral administration.¹¹

The mechanism of desensitization to trimethoprim-sulfamethoxazole and penicillin may be similar, although these immunologic changes have not been clearly described. Antigen-specific mast-cell desensitization has been proposed by some authors. Sullivan¹² and Stark et al¹³ reported the conversion of positive penicillin skin test results to negative results following oral desensitization with penicillin; however, the skin test results to irrelevant antigens remained unaffected. Further work by this group demonstrated that the mast cells retain their ability to react to some antigens, while the response to other antigens was deleted. This suggested an independent regulation and sensitivity of each antigen IgE antibody system.¹² Following desensitization, the persistence of other IgE-mediated signals indicates that tachyphylaxis to mediators such as histamine or mediator depletion does not play a significant role in the clinical response. It is not known whether adverse reactions to trimethoprim-sulfamethoxazole are IgE mediated. The successful desensitization suggests that mediator depletion does occur in these patients. Whether IgE plays a role in this process remains to be fully elucidated.

The role of antigen-specific IgG as a blocking antibody in protection against further IgE-mediated drug reactions has not been fully described. Immunoglobulin G may bind the allergenic epitopes of the drug and thus prevent binding to the mast cell.

The prevention of PCP in HIV-infected individuals has become a standard of care. The method used for prevention depends on the individual's tolerance to different treatment regimens. All the approaches produce a certain degree of adverse reactions. Aerosolized pentamidine produces coughing in 36% of patients and wheezing in 11% of patients,¹⁴ while with trimethoprim-sulfamethoxazole the main adverse reactions include hypersensitivity, gastrointestinal intolerance, and marrow suppression.³ The use of trimethoprim-sulfamethoxazole in our view offers several advantages, including low cost, ease of administration in all ages, and its broad spectrum to prevent other bacterial infections. The use of trimethoprim-sulfamethoxazole as the first-line prophylactic therapy for PCP in HIV-infected patients with CD4 cell counts of less than $0.2 \times 10^9/L$ is a reasonable one.

The small numbers and short follow-up allow us to sug-

gest that oral desensitization with trimethoprim-sulfamethoxazole may be an effective and inexpensive means to again treat patients infected with HIV with trimethoprim-sulfamethoxazole as prophylaxis against PCP. Further studies on larger groups of patients are needed to evaluate safety, efficacy, and the mechanism of response.

This study was supported in part by grant MCJ-052002-01-0 from the Office of Maternal and Child Health.

The authors gratefully acknowledge Patty Whaley and Lisa Jones for their help in the preparation of this manuscript.

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Occult Cocaine Exposure in Children

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• We determined the prevalence of cocaine and cannabinoid exposure among young children presenting to an urban pediatric emergency department without signs or symptoms suggestive of the exposure. The study included 460 children between 1 and 60 months of age in whom urinalysis was required for investigation of routine pediatric complaints. Anonymously and without informed consent, an aliquot of urine was screened for cocaine metabolite (benzoylecgonine) and 11- or Δ -9-tetrahydrocannabinol-9 carboxylic acid with the enzyme multiplied immunoassay technique. Positive specimens were rescreened with a radioimmunoassay and confirmed with gas chromatography/mass spectrometry, if a sufficient quantity of urine was available. Benzoylecgonine was identified in 25 patients (5.4%) by both screening techniques. Enough urine was available for confirmatory testing in eight patients, and all eight urine specimens contained benzoylecgonine. Neither 11- nor Δ -9-tetrahydrocannabinol-9 carboxylic acid was detected in any patient. We documented the magnitude of the problem of occult passive cocaine exposure in young children living in an urban environment. Such exposure has serious implications for the assessment of outcomes in postnatal follow-up studies of prenatally exposed children as well as potential risks to children living in household environments where occult cocaine exposure occurs.

(*AJDC*. 1991;145:1430-1432)

Cocaine use in the United States has increased dramatically during the past decade. The National Institutes on Drug Abuse reported that in 1986 cocaine became the most frequent cause of drug-related emergency department visits.¹ Changing trends in drugs of abuse among a pediatric population were studied by Soldin et al,² who described a decline in the use of cannabis but a rise in the use of cocaine from 1986 to 1988. Cocaine exposure among

certain pediatric subpopulations has been emphasized in the literature. These include adolescents,³ breast-fed infants,⁴ and neonates born to addicted mothers.^{5,6} Recent reports have identified cocaine toxicity among non-breast-fed infants and toddlers.^{7,8} Accidental ingestion and passive inhalation of free-base cocaine vapors are putative mechanisms of intoxication in this age group. Little is known regarding the prevalence of asymptomatic or unsuspected cocaine exposure in young children. Our purpose was to determine the prevalence of cocaine and cannabinoid exposure among young children presenting to an urban pediatric emergency department without signs or symptoms suggestive of the exposure.

PATIENTS AND METHODS

Our study was conducted in the emergency department of the Children's Hospital of Michigan, Detroit, an urban pediatric teaching hospital, during the period from October 1989 to December 1990. Children included were those between 1 and 60 months of age in whom urinalysis was required for investigation of one of the following chief complaints: fever, abdominal pain, genitourinary symptoms, blunt trauma, crying/fussiness, vomiting, diarrhea, or failure to thrive. Patients were excluded if exposure to drugs of abuse was suspected by history or physical examination. Anonymously and without informed consent, an aliquot of urine was tested for benzoylecgonine (BE), the major metabolite of cocaine, and 11- or Δ -9-tetrahydrocannabinol-9 carboxylic acid (THC). Anonymity was maintained by assigning a code number to each specimen that was cross-referenced to a data sheet that contained no patient identification information. This study was approved by the Children's Hospital of Michigan Institutional Review Board.

Urine samples were first screened with the enzyme multiplied immunoassay technique (EMIT) (Syva Corp, Palo Alto, Calif) with a minimal detection sensitivity of 50 μ g/L. Samples that were positive by EMIT were rescreened with a radioimmunoassay (RIA) (Abuscreen, Roche Diagnostic System, Mont Clair, NJ) that had the same sensitivity. Urine was considered positive for BE or THC only when the drug was detected by both EMIT and RIA. Confirmation of positive specimens was performed with gas chromatography/mass spectrometry (GC/MS) when a sufficient quantity of urine was available.⁹

Patient data recorded included the chief complaint, age, presence or absence of breast-feeding, day of the week at presentation, current medications, and residential zip code.

A sample size of 400 patients was calculated based on an estimated cocaine exposure rate of 1%, with an accuracy of 1% and 95% confidence. Demographics were assessed with χ^2 analysis for nominal variables and an independent t test for continuous variables.

Accepted for publication June 17, 1991.

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RESULTS

During the period of this study, 76 362 patients were cared for in the Children's Hospital of Michigan emergency department. Departmental statistics revealed that 90% of these patients were black, 8% were white, and 2% belonged to other races. Eighty percent were Medicaid or uninsured patients, while 20% had private medical insurance. Ninety-seven percent resided in Wayne County, Michigan, which encompasses the city of Detroit, while 3% resided in outlying counties. Therefore, the population from which our study sample was drawn consists of children between 1 and 60 months of age, who are predominantly black, who are covered by Medicaid or are uninsured, and who reside in an urban environment. Of this total population of patients, 460 (0.6%) were included in our study.

The cocaine metabolite BE was identified in 25 (5.4%) of 460 patients by both EMIT and RIA. Sufficient urine was available for GC/MS confirmation in eight patients, and all eight samples contained BE. The urine of one patient also contained intact cocaine, as determined by GC/MS confirmation. Neither 11- nor Δ -9-tetrahydrocannabinol-9 carboxylic acid was detected in any patient.

There was no difference in age between those patients who were positive or negative for BE (20 ± 18 vs 21 ± 17 months, $P = .7$). No cocaine-exposed patients were breast-fed. By history, six of the BE-positive patients were taking medications consisting of semisynthetic penicillins and/or acetaminophen; neither of these drugs interfere with BE or THC assays. No significant relationship was found between the day of the week and the percentage of patients exposed to cocaine ($\chi^2 = 6.3$, $P = .4$).

Patients were enrolled in the study from a catchment area of 78 zip codes. Of these, BE-positive urines were identified in 13 zip code areas. Cocaine exposure tended to be concentrated within three zip codes, in each of which more than 20% of samples obtained were positive. Demographic characteristics of these three zip code areas combined include a racial distribution of 93% black, 6% white, and 1% other; a sex distribution of 46% male and 54% female; a median age of 28.9 years, with 11% of the population younger than 6 years; a median annual household income of \$18 713; and a median number of years of school completed of 11.9.¹⁰

COMMENT

Our study demonstrated the magnitude of the problem of unsuspected cocaine exposure in young urban children. Hicks et al¹¹ previously reported 2.8% urine positivity for BE and 0% positivity for THC among 0- to 5-year-old children not suspected to have been exposed to drugs. Kharasch et al¹² found 2.5% of urine samples also obtained from children in whom drug exposure was not suspected in the same age group to be positive for BE. Our higher prevalence rate of 5.4% compared with the other studies may be due, in part, to lowering the threshold concentration for a positive screening test from 80 $\mu\text{g/L}$ to 50 $\mu\text{g/L}$ or greater. Although lowering the threshold concentration will reduce the probability of false-negative results, it also may increase the risk of false-positive results. However, this is unlikely, as specimens were only designated as positive when BE could be identified by both the EMIT and the RIA. Also, for all positive urine

samples in which sufficient quantity was available, the presence of BE was confirmed by GC/MS.

Possible routes of exposure among the infants and toddlers studied include accidental ingestion, intentional administration, and passive inhalation of cocaine vapors. Passage of cocaine from mother to infant via breast milk has been described; however, none of our BE-positive patients were breast-fed. Cocaine may be detected in the urine of newborns up to 3 to 5 days following delivery if exposure occurs in utero.¹³ All children in this study were older than 1 month of age, eliminating in utero exposure as a possible mechanism contributing to the high prevalence rate. No history of accidental ingestion or intentional administration of the drug was obtained from any of the patients included in our study. Also, no patient had signs or symptoms of drug intoxication as have been described with cocaine ingestion.^{14,15} We speculate that passive inhalation of vapors when free-base cocaine is smoked by adult caretakers is the likely mechanism of exposure in these young children.

More than 300 000 infants are born annually to women who use cocaine during pregnancy.¹⁶ Longitudinal studies of these infants have demonstrated abnormal respiratory patterns,¹⁷ sudden infant death syndrome,¹⁸ visual impairment,¹⁹ abnormal motor development,²⁰ poor reading and mathematical skills,²¹ and impaired social and emotional development.²² Although the possible contribution of continued environmental exposure to the observed problems in these infants is unknown, many of these infants live in an environment where adults regularly use cocaine. A "kindling" phenomenon has been described in which the central nervous system becomes sensitized following repeated exposure to cocaine.²³ Eventually, central nervous system stimulation occurs in response to relatively low levels of the drug. It is possible that continued environmental exposure to cocaine may influence the results of long-term follow-up studies of infants exposed to cocaine in utero. This should be considered in future follow-up studies of such infants.

The prevalence of unsuspected cocaine exposure in infants and toddlers revealed by our study is indeed alarming. Physicians must be aware of this high-risk pediatric subpopulation, particularly those who practice in areas where cocaine use is epidemic. Parental education concerning the possibility of inhalational cocaine exposure may be important. However, the potential deleterious effects of such exposure remain to be determined.

This work was funded in part by the European Endorsement Fund of the Children's Hospital of Michigan (Dr Meert).

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The Incidence of Prenatal Brain Injury

A series of 165 brains of infants who were stillborn or who died shortly after birth were examined to identify the incidence and nature of prenatal brain damage. Forty-four percent of the stillborn infants showed evidence of brain damage thought to be related to circulatory disorders, primarily ischemic damage to cerebral white matter. Of 90 liveborn infants, 36% had prenatal ischemic damage.

Once again, a modern neuropathologic study has shown that prenatal factors are probably far more important in causation of cerebral palsy than previously assumed.

Squier M, Keeling JW. The incidence of prenatal brain injury. *Neuropathol Appl Neurobiol*. 1991;17:29-38.

Frequency of Infections Associated With Implanted Systems vs Cuffed, Tunneled Silastic Venous Catheters in Patients With Acute Leukemia

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• A total of 75 central venous catheters were used for prolonged chemotherapy in 39 children with acute lymphocytic leukemia and 21 patients with acute myelocytic leukemia. Infection rates were 2.2 per 1000 catheter days with the use of cuffed, tunneled, single-lumen Silastic catheters, 2.0 per 1000 catheter days with cuffed, tunneled, double-lumen Silastic catheters, and 0.5 per 1000 catheter days with the use of implanted venous access systems. Eighty-one percent of catheter sepsis episodes were successfully treated without removal of the catheter. All tunnel infections required withdrawal of the catheter for cure. The microorganisms were gram-positive bacteria in 15%, gram-negative bacteria in 7%, and fungi in 4%. Coagulase-negative staphylococci and *Pseudomonas aeruginosa* were the most commonly isolated organisms. Three of six fatal sepsis episodes were caused by disseminated fungal infections. We conclude that the use of intracorporeal venous catheter systems in patients with acute lymphocytic leukemia is associated with a lower infection rate than that with cuffed, tunneled Silastic single- or double-lumen catheters and that most septicemias can be cured with antimicrobial therapy without removal of the catheter.

(AJDC. 1991;145:1433-1438)

Since the introduction of cuffed, tunneled Silastic catheters by Broviac et al¹ in 1973 and Hickman et al² in 1979, the treatment of pediatric oncology patients requiring prolonged central venous access for total parenteral nutrition and intensive chemotherapy has markedly improved. However, catheter-related infections are a major problem in pediatric patients with cancer. In addition, thrombotic occlusions, dislocations, and other mechanical complications are common. Meticulous care in regular sterile gauze dressing changes and daily heparin-saline flushes of the external catheter seems to be critical for reducing the incidence of catheter complications during hospital or outpatient management.

In recent years, totally implanted central venous catheter systems have been employed in children with malignant disease for prolonged chemotherapy. Reported

infection rates suggest that intracorporeal venous access systems may be associated with a lower risk of infection than external venous catheters. However, studies with implanted catheter systems in pediatric oncology patients are scarce, and the various neoplastic diseases usually included may be associated with different infection rates. Children with leukemia are at a particular high risk for infection. Neutropenia, whether related to the primary disease or a consequence of chemotherapy, seems to be the most important predisposing factor.^{3,5} In addition, qualitative abnormalities of neutrophil function, including defects of chemotaxis, phagocytosis, or bactericidal activity, have been described even with a normal number of circulating leukocytes.^{6,8}

We reviewed the experience during a 7½-year period with intracorporeal venous access systems and cuffed, tunneled single- or double-lumen Silastic catheters in our pediatric patients with acute lymphocytic and myelocytic leukemia.

MATERIALS AND METHODS

Hospital and outpatient records of the Oncology Division of Children's Medical Center at Dallas, University of Texas, were reviewed to identify all patients with acute leukemia selected for insertion of a central venous catheter for chemotherapy between January 1983 and July 1990. Catheters were inserted, with the patient under general anesthesia in the operating room, by external jugular, cephalic, or facial vein cutdown or subclavian puncture. Cuffed, tunneled venous catheters were inserted according to described methods⁹ and included 20-F Cook double-lumen catheters. In addition, five noncuffed catheters, consisting of two percutaneous plastic, two Silastic, and one unspecified central venous catheters, were placed. Sterile film and iodophor solution dressings were applied to the exit site wound. The catheter care protocol consisted of cleaning and disinfection of the exit site twice a week by the nursing personnel and by the parents at home after being instructed in catheter care by the nursing staff. Capped catheters were filled with heparin-saline solution (100 U/mL) daily and after infusion.

Twenty-five Port-a-Cath and one Mediport systems were implanted for central venous access. Fluoroscopy was used to confirm the position of the tip of each catheter after placement. Thereafter, the reservoir and catheter were flushed with heparinized saline once every month and after each use for chemotherapy. Medical records of all patients were studied for sex, race, age at diagnosis of leukemia, and classification of leukemia

Accepted for publication June 10, 1991.

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Reprints not available.

Table 1.—Study of 75 Central Venous Catheters in 60 Pediatric Patients With Acute Leukemia

Type of Catheter	No.	Duration, d		No. of Catheter-Related Infections			No. of Infections/1000 Catheter Days	Other Complications, No.		
		Range	Total	Septic	Local	Both		Malposition	Occlusion	Leak
Tunneled, cuffed, single-lumen Silastic	19	6-1207	5477	9	3	0	2.2	4	3	1
Tunneled, cuffed, double-lumen Silastic	26	4-962	6570	10	1	2	2.0	1	4	0
Implanted venous access system	25	7-1062	9611	4	1	0	0.5	1	0	1
Other*	6	32-629	1382	0	1	0	0.7	0	1	0
Total	75	4-1207	23 040	23	6	2	1.3	6	8	2

*Two percutaneous plastic catheters, one percutaneous noncuffed, nontunneled Silastic catheter, one tunneled, noncuffed Silastic catheter, and one unspecified catheter.

as lymphocytic and myelocytic. Catheter duration was defined as the time interval from the day of insertion to the day of withdrawal of the catheter, death of the patient, or last hospital visit during the study period with the catheter infection. The end of the infection-free interval also included the day of catheter removal for reasons other than infection, death of the patient with an uninfected catheter, or the last hospital visit with the catheter still in use.

Nonquantitative blood cultures from a peripheral vein and from the catheter were performed in conventional blood culture broth when sepsis was suspected. Sepsis was classified as catheter related when fever (temperature, $>38^{\circ}\text{C}$) and at least one positive culture of blood, whether from peripheral veins, through the catheter, or both, was present and no other focus could be identified as a source of septicemia. Sepsis was considered to be cured when clinical signs resolved and at least one blood culture during or after treatment was negative. Neutropenia at the presentation of the infection was defined as an absolute granulocyte count of less than $500/\text{mm}^3$.

Empiric parenteral antibiotic therapy was started immediately in the neutropenic febrile patient after the cultures were taken. Nonneutropenic patients were hospitalized and treated either when sepsis was suspected or when a positive blood culture was obtained. Catheter-related local infections at the exit site, in the tunnel, or in the subcutaneous pocket required for definition that progressive cutaneous or subcutaneous inflammatory signs with or without exudate were present.

Chemotherapy according to the Dallas-Fort Worth Pediatric Oncology Group protocols for lymphocytic and myelocytic leukemia was given to the majority of patients. The induction and consolidation phases represented periods of approximately 1 and 3 months, respectively, when the patients received more immunosuppressive treatment than during the following maintenance phase of chemotherapy.

Statistical analysis was performed by Wilcoxon signed rank test for two independent samples. $P < .05$ was considered significant.

RESULTS

Seventy-five central venous catheters were inserted for chemotherapy in 60 children with acute leukemia. There were 46 catheters in 39 patients with acute lymphocytic leukemia and 29 catheters in 21 children with acute myelocytic leukemia. At diagnosis, the mean age of the 33 boys and 27 girls was $6\frac{1}{2}$ years, with a range of 8 months to 16 years. There were 47 white, five black, and eight Hispanic children. A single catheter was inserted in 49 patients (82%), two catheters were placed in nine patients (15%), one patient required three catheters, and one patient required five catheters.

Thirty-two catheters were removed, 14 catheters remained in place until death, and 29 catheters were still in

use at the last hospital visit. Of the 75 central venous catheters implanted for chemotherapy, 19 were cuffed, tunneled, single-lumen catheters; 26 were cuffed, tunneled, double-lumen catheters; 25 were implanted venous access systems; and five were noncuffed catheters.

Nineteen cuffed, tunneled, single-lumen catheters were placed in patients at a mean age of 77 months, with a mean duration of 288 days. Nine were removed, five remained in place until death, and five were still in use at the last hospital visit. Of 26 cuffed, tunneled, double-lumen catheters implanted at a mean age of 82 months, with a mean duration of 253 days, 15 catheters were removed, five remained in place until death, and six were still functioning. Of 25 intracorporeal venous access devices placed at a mean age of 81 months, with a mean duration of 384 days, 17 were still in use, five had been removed, and three were in place when the patients died.

Of the 32 central venous catheters that required removal (43%), seven had thrombotic occlusions, nine had catheter-related infections, and 16 were removed for other reasons (dislocation, leakage, or end of chemotherapy). Of the seven episodes of thrombotic occlusions, only one episode was reversible after flushing with urokinase. The interval between placement and obstruction of the catheter ranged from 4 to 164 days, with a mean of 66 days. No thrombotic obstruction was reported in intracorporeal venous access systems. The incidence of catheter-related mechanical complications other than infections was 1.46 per 1000 catheter days in cuffed, tunneled, single-lumen catheters; 0.76 per 1000 catheter days in cuffed, tunneled, double-lumen catheters; and 0.21 per 1000 catheter days in implanted catheter systems (Table 1).

Overall, 30 septic episodes occurred in 26 patients during central venous catheter use. Fifteen patients (68%) had one, six patients two, and one patient three sepsis episodes. According to the source of infection, the distribution of the 60 patients with central venous catheters was as follows. Thirty patients (50%) had no catheter-related infection or non-catheter-related sepsis; 25 patients (42%) had catheter-related infections (septic and/or local) only; one patient had a local catheter-related episode and a non-catheter-related septic episode; and three patients (5%) had only non-catheter-related septic episodes.

Of the 27 patients with catheter-related infections, 20 (74%) had sepsis, five (19%) had local catheter infections, and two (7%) had combined sepsis and local infections. Five children with five septic episodes had identified

Table 2.—Organisms Isolated From Blood and Catheter Exit Site in 30 Patients

Organism	No.			Total
	Catheter-Related Infections		Non-Catheter-Related Sepsis	
	Sepsis	Local		
Gram-positive bacteria				
Coagulase-negative staphylococci	5 (1*)	1*	0	6
<i>Staphylococcus aureus</i>	4	3 (1,* 2†)	0	7
<i>Streptococcus</i> , viridans group	2	0	0	2
Other streptococci	1	0	0	1
<i>Bacillus</i> species	2	0	0	2
<i>Clostridium butyricum</i>	1	0	0	1
Total	15	4	0	19
Gram-negative bacteria				
<i>Pseudomonas aeruginosa</i>	5	1*	0	6
<i>Klebsiella pneumoniae</i>	2 (1*)	0	1	3
<i>Enterobacter aerogenes</i>	0	1*	0	1
<i>Shigella</i> species	0	0	1*	1
<i>Citrobacter freundii</i>	0	0	1*	1
<i>Escherichia coli</i>	0	0	1	1
<i>Haemophilus influenzae</i> , type b	0	0	1	1
Total	7	2	5	14
Fungi				
<i>Candida tropicalis</i>	2	0	1	3
<i>Candida albicans</i>	1	0	0	1
<i>Candida parapsilosis</i>	1	0	0	1
Total	4	0	1	5

*Mixed culture.

†Combined septic and exit wound infection.

sources other than the catheter: perianal abscess (*Escherichia coli*), perirectal abscess (mixed culture of *Shigella* species and *Citrobacter freundii*), pneumonia in two patients (*Haemophilus influenzae* type b and *Klebsiella pneumoniae*), and erosive esophagitis (*Candida tropicalis*).

Local catheter infections consisted of two exit wound infections, two tunnel infections, one exit wound and tunnel infection, and one pocket infection. Neutropenia and fever were present in half of the episodes. In only two of the six cases could organisms be isolated: *Pseudomonas aeruginosa* and a mixed culture of *Staphylococcus aureus*, coagulase-negative staphylococci, and *Enterobacter aerogenes*. The infection-free interval ranged from 2 to 564 days. Five of six local catheter infections occurred during the induction or consolidation phase of chemotherapy. Oral antibiotic therapy was given to one patient, and five patients received intravenous antibiotic treatment for 7 to 28 days. Removal of the catheter was required for cure of three tunnel infections and one exit wound infection. In two episodes of combined sepsis and local infection, *Staphylococcus aureus* was isolated and intravenous antibiotic treatment was given for 7 and 28 days; removal of the catheter was required for successful treatment in one case. The infection-free interval was 70 and 41 days, and both infections occurred during the consolidation phase of chemotherapy.

Twenty-two patients had 25 septic episodes without an identified source other than the catheter. Peripheral-vein

and catheter blood cultures were positive in 14 episodes, catheter blood culture only in seven cases, and peripheral blood culture only in four episodes. Gram-positive bacteria were isolated in 58%, gram-negative bacteria in 27%, and fungi in 15% of cases (Table 2). Coagulase-negative staphylococci and *P aeruginosa* were the most frequently isolated single organisms. Neutropenia was present in 19 (76%) of 25 septic episodes. Seventeen (68%) of the 25 episodes occurred during the induction or consolidation phase of chemotherapy.

Although the infection rate for cuffed, tunneled Silastic catheters was higher in acute myelocytic than in lymphocytic leukemia, with 2.6 vs 1.7 infections per 1000 catheter days, the difference was not statistically significant ($P=.25$). Twenty-six catheters used in 21 patients with myelocytic leukemia at a mean age of 94 months had a total duration of 5450 days, whereas 19 catheters inserted in 16 patients with lymphocytic leukemia at a mean age of 61 months had a total duration of 6597 days. Twenty-four intracorporeal venous access systems implanted in 23 children with acute lymphocytic leukemia at a mean age of 80 months had a total duration of 9604 days and 0.3 infection per 1000 catheter days. This was a significantly lower infection rate ($P=.025$) than that for cuffed, tunneled Silastic catheters used in patients with acute lymphocytic leukemia. Only one Port-a-Cath was placed in a child with acute myelocytic leukemia.

Overall, seven (50%) of 14 catheter-related infections in

Table 3.—Studies of Totally Implanted Central Venous Access Devices in Pediatric Oncology Patients

Source, y	Location	No. of Patients	No. of Catheters	No. of Infections/ 1000 Catheter Days
Pegelow et al, ¹¹ 1986	Miami, Fla	15	16	0.97
McGovern et al, ¹³ 1985	San Antonio, Tex	39	NI*	0.4
McDowell et al, ¹⁰ 1986	Liverpool, England	12	12	2.3
Shulman et al, ¹² 1987	Houston, Tex	31	33	0.66
Present report	Dallas, Tex	24	25	0.52

*No information.

Table 4.—Studies of Cuffed, Tunneled Silastic Catheters in Pediatric Oncology Patients

Source, y	Location	No. of Patients	No. of Catheters	No. of Infections/ 1000 Catheter Days
Merrit et al, ¹⁴ 1981	Los Angeles, Calif	18	21	2.21
Shapiro et al, ¹⁵ 1982	Pittsburgh, Pa	27	31	2.68*
Darbyshire et al, ¹⁶ 1985	Bristol, England	36	49	6.99
King et al, ¹⁷ 1985	Columbus, Ohio	88	NI†	1.37*
Gilman et al, ¹⁸ 1986	Morgantown, WV	16	21	1.33
Cairo et al, ¹⁹ 1986	Irvine, Calif	46	53	3.40
Johnson et al, ²⁰ 1986	Nashville, Tenn	64	70	2.84
Hartman and Shochat, ²¹ 1987	Stanford, Calif	50	63	2.56
Viscoli et al, ²² 1988	Genoa, Italy/London, England	145	157	0.68
Present report	Dallas, Tex	37	46	2.07

*Catheter-related local infections not determined.

†No information.

patients with acute lymphocytic leukemia and 15 (87%) of 17 infectious episodes in patients with acute myelocytic leukemia occurred during the induction and consolidation phases of chemotherapy.

Intravenous antibiotic therapy was given for a mean duration of 10 days. The infection-free interval in the 50 uninfected catheters was 15 733 days, with a mean of 314 days; in the 25 infected catheters, it was 3473 days, with a mean of 139 days. After four patients who died of sepsis were excluded, 17 (81%) of the remaining 21 catheter-related septic episodes were cured without removal of the catheter. In four septic episodes with isolation of *S aureus*, *Bacillus* species, *P aeruginosa*, and *C tropicalis*, the central venous catheter required removal to cure the infection.

Fourteen patients died during the study period, six in association with sepsis and one with pneumonia. *Candida tropicalis* was isolated from the lung culture of the patient with pneumonia. In two of six fatal septic episodes, a perirectal abscess (*Shigella* species) and an erosive esophagitis (*C tropicalis*) were found at autopsy. Disseminated fungal infections were responsible for three and gram-negative organisms for the other three of the fatal infections. The sepsis-free interval was variable and ranged from 25 to 315 days. Neutropenia was present in all fatal episodes, and two of three occurred during the induction or consolidation phase of chemotherapy.

COMMENT

Sepsis and pocket infection rates of implanted venous access systems in this study were in the lower range of comparable studies,¹⁰⁻¹² which showed 0.49, 0.53, and 1.89 septic episodes and 0.0, 0.47, and 0.49 pocket infections

per 1000 catheter days, respectively. In three of four studies, the overall catheter infection rate in pediatric oncology patients receiving chemotherapy through totally implanted venous access systems was lower than one per 1000 catheter days¹⁰⁻¹³ (Table 3). However, in one study an infection rate of 2.3 per 1000 catheter days was found,¹⁰ suggesting that different factors, such as catheter care, intensity of catheter use, and hospital vs home therapy, might contribute to a higher infection rate. No mortality related to sepsis was reported.

Studies with cuffed, tunneled Silastic catheters in pediatric oncology patients¹⁴⁻²² (Table 4) showed infection rates between 0.68 and 3.4 per 1000 catheter days^{14,16,19,21,22} with the exception of one report of 6.99 infections per 1000 catheter days.¹⁶

Successful antimicrobial therapy with the vascular catheter kept in place occurred in 81% of septic episodes and in 63% of all infections related to central venous catheters. In nine studies with pediatric cancer patients and cuffed, tunneled Silastic catheters, between 57% and 100% of catheter infections were treated and cured without removal of the catheter.^{16-19,21,23} However, some investigators considered catheter sepsis cured only if the same organism did not recur after completion of antibiotic therapy. Difficulty in clearing tunnel infections without removing the catheter has been reported by several investigators and may reflect poor antibiotic penetration or lack of drainage.^{24,25} *Candida* and *Bacillus* species, isolated in two of our septic episodes that required catheter removal for cure, are traditionally considered difficult to eradicate with the catheter kept in place.^{17,25-28} *Candida* species have the ability to adhere to host cells and plastic

surfaces, and, on electron microscopy, naturally infected catheters show adherent *Candida* enmeshed with fibrin strands.²⁹ Persistent adherence and colonization of catheters may be facilitated by reduced phagocyte activity in this microenvironment.^{29,30}

Although the infection of the catheter lumen or tunnel might occur during implantation or by hematogenous seeding from bacteremia,³¹ the mechanism of contamination of these devices is not always clear. Coagulase-negative staphylococci, a frequent cause of catheter-related septic and local infections, are able to produce an extracellular slime substance that limits penetration of antibiotics and drastically reduces the inflammatory host response, facilitating bacteriologic growth at the inner and outer slime surface.^{20,32-34} Although coagulase-negative staphylococci are common contaminants in blood cultures, even a single isolation of this organism in a patient with a central venous catheter must be taken seriously,³⁵⁻³⁷ especially in neutropenic patients.^{5,28,38-40}

Some investigators have noted a change in the spectrum of microorganisms isolated from blood of oncology patients using central venous catheters rather than peripheral venous catheters in the last 10 to 15 years.⁴¹⁻⁴³ This study showed no consistent predominance or shift to gram-positive organisms in septicemia during a 7½-year period. However, the limited number of blood isolates allows no definite conclusions.

The clinical diagnosis of central venous catheter sepsis in pediatric oncology patients is difficult. There is a wide variation in categorizing a septic infection as catheter related. Some studies have counted all febrile episodes, all bacteremia, or all culture-proved septic infections. Most have required that there be no evidence of an alternative focus of infection.^{17,19,21,44} Although the distinction between catheter-related and non-catheter-related septicemia may not be critical for the choice of antimicrobial therapy, some investigators have recommended quantitative blood cultures drawn through the catheter and from a peripheral vein to permit a more precise diagnosis and facilitate the decision of the clinician about whether catheter sepsis might be successfully treated without removal of the catheter.^{27,41} The use of comparative quantitative blood cultures currently represents the most accurate method for identifying catheter-related sepsis; however, appropriate processing of such cultures depends on careful collaboration with the clinical microbiology laboratory.

In terms of mechanical complications of cuffed, tunneled Silastic catheters, comparable studies in pediatric oncology patients showed rates between 0.23 and 2.21 thrombotic occlusions per 1000 catheter days.^{16,19,21,22} Thrombosis occlusion rates in three studies¹¹⁻¹³ with implanted venous access devices in pediatric oncology patients ranged from 0.3 to 0.53 per 1000 catheter days, and one report showed no occlusion during 2117 catheter days.

We conclude that implanted venous catheter systems in pediatric patients with leukemia not only offer advantages in terms of catheter care and psychological acceptability but also have substantially lower infection rates and longer duration than cuffed, tunneled Silastic catheters in patients with acute lymphocytic leukemia. Whether this is also true for patients with acute myelocytic leukemia remains to be analyzed in future studies. We believe that intracorporeal venous access devices should be preferred in all children with acute lymphocytic

leukemia considered for chemotherapy through a central venous catheter.

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Mismatch Between Pediatric Training and Pediatric Practice: An Australian View

A questionnaire was sent in 1985 to 232 Australian pediatricians asking whether they had seen an increase or decrease in "the new morbidity" in the previous 5 years. Striking increases were reported in numbers of patients presenting with behavior problems, developmental delay, learning and school problems, and adolescent health and behavior problems. While the pediatricians considered their training in the traditional subspecialty areas of infectious disease, respiratory medicine, and gastroenterology to have been appropriate, they believed their training in the new morbidity areas had been inadequate, especially in behavioral pediatrics, adolescent medicine, parental counseling, and the care of children with chronic handicaps.

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Radiological Case of the Month

Michael P. Mah, MD; Jonathan S. Fain, MD; Sue L. Hall, MD (Contributors);
Beverly P. Wood, MD (Section Editor)

A male newborn, born at 41 weeks' gestation and weighing 3230 g, presented on the first day of life with complex cyanotic heart disease, including the following signs: double-outlet right ventricle, mitral atresia with hypoplastic left ventricle, and hypoplastic aortic arch with coarctation. He was transferred to a level-3 nursery at age 12 days. He underwent pulmonary artery banding, repair of the coarctation of the aorta, and ligation of a patent ductus arteriosus. Congestive heart failure continued after surgery, and the patient was maintained on total parenteral nutrition administered through a double-lumen femoral venous catheter that had been placed during surgery. Eleven days after surgery, he was pale, poorly perfused, and tachypneic.

A septic workup was performed and cultures of blood, urine, and cerebrospinal fluid were obtained.

From the Departments of Pediatrics (Drs Mah and Hall) and Pathology (Dr Fain), University of California-Los Angeles Medical Center, Los Angeles, CA.

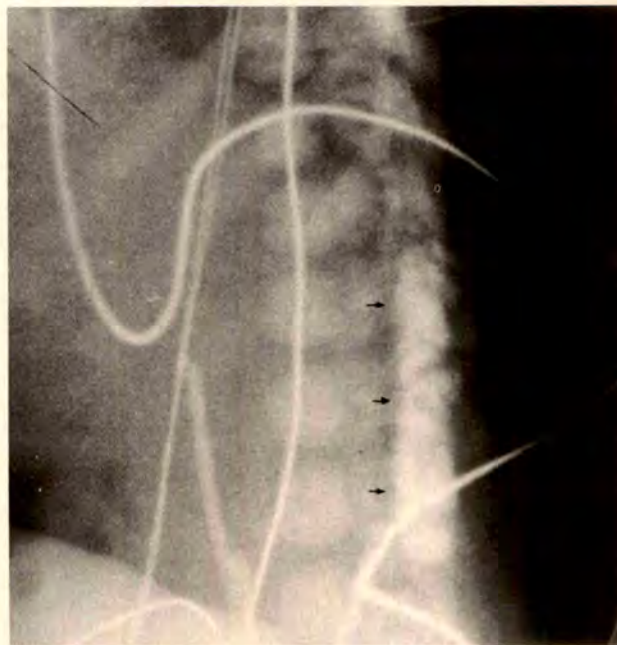
Reprint requests to the Department of Radiology, Box 81, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90054-0700 (Dr Wood).

Attempted lumbar puncture using a 22-gauge spinal needle, introduced at the L3-4 interspace, yielded 4 mL of milky white fluid. Cefotaxime and vancomycin therapy was started immediately. The following laboratory values were obtained from the lumbar puncture specimen: glucose, 1268 mmol/L; protein, 4.8 g/L; red blood cell count, $132 \times 10^6/L$; and white blood cell count, $99 \times 10^6/L$. Gram staining was negative for organisms and bacterial antigens representing *Neisseria meningitidis* (groups A, B, C, Y, and W135), *Streptococcus pneumoniae*, *Haemophilus influenzae* (type b), and group B *Streptococcus*. Total parenteral nutrition consisting of 22.5% dextrose and 20% lipid emulsion, which was infused into one of the two lumens of his femoral venous catheter, was discontinued. A low-osmolality contrast medium was injected into the same lumen of the femoral line and a frontal roentgenogram obtained (Fig 1). Forty-five minutes later, a contrast medium was again injected, with the results shown in Fig 2. The femoral venous line was removed. A lumbar puncture 3 days later yielded normal cerebrospinal fluid. The patient was eventually discharged without apparent neurologic or infectious sequelae.

Figure 1.



Figure 2.



Denouement and Discussion

Intravenous Hyperalimentation Fluid Obtained With Lumbar Puncture: An Unusual Complication of a Central Venous Catheter

Fig 1.—Frontal roentgenogram of abdomen shows retrograde flow of contrast medium from the inferior vena cava through a lumbar vein (arrow) into the epidural venous plexus.

Fig 2.—Lateral abdominal roentgenogram demonstrates contrast medium located in the epidural venous plexus (arrows) anterior to the subarachnoid space.

Central venous catheters are important for adequate medical management of severely ill neonates and children. Although usually safe, complications of central venous catheters do occur. Reported complications include pneumothorax, hydrothorax, pulmonary embolus, sepsis, caval thrombosis, and intracardiac catheter-tip thrombus formation.¹ This case represents an unusual complication. There was preferential flow of total parenteral nutrition from the side port of the central venous catheter into a lumbar vein, with consequent progression into and distension of the epidural venous plexus. This complication was attributed to catheter thrombosis. The recovery of "milky cerebrospinal fluid" from the lumbar puncture constituted recovery of total parenteral nutrition

from the venous plexus superficial to and surrounding the spinal canal. The cerebrospinal fluid contained no contrast material, as distinguished with roentgenography.

To our knowledge, there is one previous report² of a lumbar puncture yielding milky fluid with an extremely high glucose and protein content in an infant receiving hyperalimentation. That case differs from ours in that a postmortem barium study showed the catheter had entered an ascending lumbar vein. Free barium extravasated into the epidural space and retroperitoneum. As in our case, roentgenography did not demonstrate entry of the contrast medium into the cerebrospinal fluid.

A markedly elevated level of protein and glucose from a lumbar puncture specimen in an infant receiving central venous hyperalimentation should alert the physician to the possibility that a misplaced or thrombosed catheter has allowed retrograde venous flow of parenteral fluid into the epidural venous plexus surrounding the spinal canal. Both this case and the previous report illustrate the importance of confirming catheter position by injection of the catheter as part of a roentgenographic contrast study.

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Picture of the Month

Walter W. Tunnessen, Jr, MD (Contributor and Section Editor)



Figure 1.



Figure 3.



Figure 2.



Figure 4.

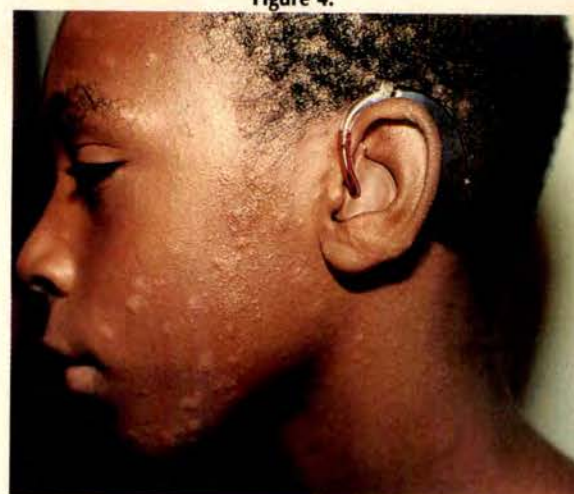


Figure 5.

Accepted for publication March 15, 1991.
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Denouement and Discussion

Pityriasis Rosea

Fig 1.—Typical, ovoid plaques of pityriasis rosea with fine scales.

Fig 2.—Multiple pink plaques of pityriasis rosea are arranged in lines of skin cleavage, producing a fir-tree type of configuration.

Fig 3.—Giant, confluent plaques of pityriasis rosea bear little resemblance to the classic lesions.

Fig 4.—Diffuse, small papules of pityriasis rosea obscure a larger plaque.

Fig 5.—Inverse pityriasis rosea with lesions primarily located on the face and extremities.

Manifestations

Pityriasis rosea (PR) commonly occurs in children and young adults. The classic appearance, ovoid plaques arranged with their long axes following skin cleavage lines, creating a pine-bough or fir-tree configuration, is easily recognized by most physicians. The rash of this disorder is much more variable than most suspect, resulting in missed diagnoses, unnecessary laboratory tests, and referral to dermatologists. The figures illustrate the typical lesions and some of the variability seen with this common eruption.

The label applied to dermatologic disorders often describes the clinical picture. Pityriasis means a fine scale and rosea means pink. The rash, then, is characterized by pink lesions with fine scales. The lesions of pityriasis rosea occur most commonly on the trunk. A single lesion, the herald patch, may precede the appearance of the secondary rash by 7 to 14 days. The patch occurs most frequently on the trunk and may be as large as 10 cm in diameter. Its prevalence is varied, but it probably precedes the diffuse rash in less than 50% of cases.

The typical, later appearing lesions are elliptical and average 1 cm in diameter. They are macular or slightly raised plaquelike lesions with pink or brownish bases. The fine scales covering the lesion may be made more apparent with light scratching. Papules of 1 to 2 mm may be so prominent that the plaques are "concealed." The typical fir-tree configuration of the rash is best appreciated by observing the back from a distance of 1.2 to 1.8 m.

Coalescent gigantic plaques may also conceal the fir-tree pattern. Lesions sometimes can have an urticarial nature. Vesicular or bullous forms are rarely recognized as PR. The appearance of the palms and soles may be similar to that of subjects with dyshidrosis, or there may be a varicellalike appearance if the vesicles are widespread.¹ A rare hemorrhagic character and an erythema multiforme-like appearance have been described.^{2,3} Oral lesions of various types, including erythematous plaques, hemorrhagic puncta, and ulcers, have also been reported.⁴

Two unusual patterns of PR are noteworthy. The typical secondary lesions appear over areas generally spared, such as the face and extremities, and remarkable sparing of the trunk occurs in the inverse type of PR. There is also a less commonly recognized localized form producing lesions that may occur only on the lower abdomen, the inguinal area, one axilla, the neck, or one part of the face.

The prolonged course of PR needs to be explained to affected patients. The secondary rash generally develops over 2 weeks, persists for another 2 weeks, and fades over another 2 weeks for an average duration of 6 weeks. However, lesions have persisted for as long as 3 to 4 months.

The lesions of PR are most frequently confused with tinea corporis, nummular eczema, and drug eruptions. Guttate psoriasis and tinea versicolor occasionally may have similar presentations. The rash of secondary syphilis may almost be indistinguishable from PR, in which case serologic testing may be necessary for proper diagnosis.

Pityriasis rosea is more common in the fall, winter, and spring. About 75% of cases occur in subjects aged 10 to 35 years, but a 3-month-old has been reported to have this rash. The cause of PR is unknown, but it is believed to be the result of an infectious, probably viral, process. Small epidemics and family outbreaks have been reported. There are usually no prodromal symptoms to call attention to the disorder. Recurrences are uncommon, probably occurring in less than 3% of affected individuals. There is no reason to exclude children with PR from school.

Treatment

The most common symptom associated with PR is pruritus, which occurs in up to 75% of those affected. Because the disorder is self-limited, pruritus is generally the only symptom that requires attention, and then only if the individual is uncomfortable. Some recommend a mild topical steroid or an emollient with 0.25% menthol to control this symptom. An oral antipruritic agent is rarely required.

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The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Tunnessen (Picture of the Month), The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104, or Dr Wood (Radiological Case of the Month), Department of Radiology, Children's Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

AMERICAN JOURNAL OF DISEASES OF CHILDREN

AJDC

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Volume 145

January through December 1991

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PEDIATRICIAN - Seeking BC/BE MD or DO pediatrician for full-time faculty position with clinical and academic responsibilities. Send CV to: Lawrence E. Jacobson, DO, Dean for Academic Affairs, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312.

THE OHIO STATE UNIVERSITY Department of Pediatrics is seeking a board-certified/board-eligible neonatologist. Responsibilities include patient care, teaching and research in an academically oriented children's hospital. The position is a full-time academic position. Competitive salary and benefits. Applicants should send curriculum vitae to: James A. Menke, MD, Associate Professor, Department of Pediatrics, The Ohio State University, 700 Children's Drive, Columbus, OH 43205. The Ohio State University is an affirmative action/equal opportunity employer.

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The candidate should be a dynamic individual with strong leadership qualities, in clinical, teaching and research endeavors. Appointments will be at the Associate or full Professor level.

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References: 1. Sandler RB, et al: *Am J Clin Nutr* 1985;42:270-274. 2. Rubin K: *Pediatric By-Line* 1985;4(3):1, 4-6. 3. Marston R, Raper N: *National Food Review* 1987;36:18-23. 4. Heaney RH: *The Physician and Sportsmedicine* 1987;15:83-88.



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Volume 146, Number 2

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Indications and Usage: Augmentin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower Respiratory Tract Infections caused by β -lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.
Otitis Media caused by β -lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.

Sinusitis caused by β -lactamase-producing strains of *Hemophilus influenzae* and *Moraxella catarrhalis*.

Skin and Skin Structure Infections caused by β -lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.
Urinary Tract Infections caused by β -lactamase-producing strains of *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.

While Augmentin is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to Augmentin treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β -lactamase-producing organisms susceptible to Augmentin should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to Augmentin, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to Augmentin when there is reason to believe the infection may involve any of the β -lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, AUGMENTIN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Precautions: General: While Augmentin possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with Augmentin may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of allergic rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with Augmentin and allopurinol administered concurrently.

Augmentin should not be co-administered with Anabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Augmentin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of Augmentin in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when Augmentin is administered to a nursing woman.

Adverse Reactions: Augmentin is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were: diarrhoea/loose stools (3%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black hairy tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthralgia/myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactoid) reactions can occur with oral penicillin (See WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with Augmentin. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic/hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with Augmentin.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage and Administration: The Augmentin 250 mg tablet and the 250 mg chewable tablet do not contain the same amount of clavulanic acid (as the potassium salt). The Augmentin 250 mg tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the Augmentin 250 mg tablet and the 250 mg chewable tablet should not be substituted for each other, as they are not interchangeable.

Since both the Augmentin 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two Augmentin 250 mg tablets are not equivalent to one Augmentin 500 mg tablet. Therefore, two Augmentin 250 mg tablets should not be substituted for one Augmentin 500 mg tablet for treatment of more severe infections.

Dosage: Adults: The usual adult dose is one Augmentin 250 mg tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one Augmentin 500 mg tablet every eight hours.

Children: The usual dose is 20 mg/kg/day based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and lower respiratory tract infections, the dose should be 40 mg/kg/day based on the amoxicillin component, in divided doses every eight hours. Severe infections should be treated with the higher recommended dose.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

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